APRIL 1950

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

PRESENT STATUS OF CORTISONE AND ACTH

A Symposium

CLINICAL RESEARCH MEETING

Abstracts

—Distinguished HOEBER Books—

✓ **Coley's NEOPLASMS OF BONE**

A truly authoritative presentation of the clinical aspects of bone tumors.

By Bradley L. Coley, M.D., *Memorial Hospital, N.Y.C.*, 779 pp., 622 illus., 53 tables, $17.50.

✓ **Berliner's BIOMICROSCOPY OF THE EYE**

A combination textbook, atlas and clinical guide to diagnosis of the living eye. Second volume now available.

By Milton L. Berliner, M.D., *Cornell Univ. Med. College*, 1540 pp., 1233 illus., 508 in full color, Vol. II, $35.00, 2-Volume Set complete, $50.00.

✓ **Mettler's SELECTIVE PARTIAL ABLATION OF THE FRONTAL CORTEX**

The complete, official report of the Columbia-Greystone study of the effects of topectomy.

By The Columbia-Greystone Associates, Fred A. Mettler, M.D., *Editor*, 681 pp., 125 illus., $10.00.

Order From Your Bookseller or On Approval From the Publishers

---

PAUL B. HOEBER, INC.

Medical Book Department of Harper & Brothers

49 EAST 33rd STREET, NEW YORK 16, N. Y.

Announcing an

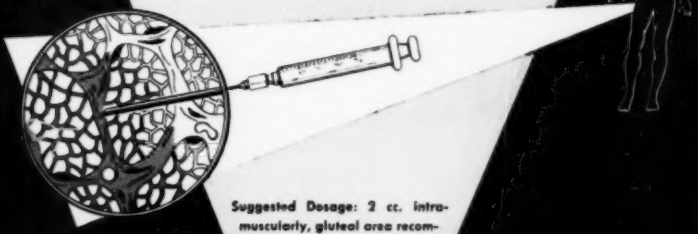
Aqueous Alpha-Tocopherol

EPSILAN PHOSPHATE

(d,l — Alpha-Tocopherol Monosodium Phosphate, Warren-Teed)

100 mg. (50 mg. per cc. in 2 cc. ampuls, boxes of 12 or 25)

High solubility encourages rapid and complete absorption . . . particularly important in emergency cases. EPSILAN PHOSPHATE Warren-Teed contains no other ingredients, is non-toxic.



Suggested Dosage: 2 cc. intramuscularly, gluteal area recommended . . . repeat according to requirements of the patient as determined by the physician.

WARREN-TEED *Pharmaceuticals*

THE WARREN-TEED PRODUCTS COMPANY • COLUMBUS 8 • OHIO

pruritus

minimized

this new way . . .

Insect bites, pruritic and allergic skin disorders usually are promptly relieved with Thephorin Ointment. This effective topical agent supplies the new and entirely different antihistamine, Thephorin, in a Carbowax base for a convenient new way of minimizing pruritus. In a typical clinical trial*, more than 75% of 305 patients with various allergic and pruritic skin disorders were relieved by Thephorin Ointment. Available in 1½-oz collapsible tubes and 1-lb jars.

HOFFMANN-LA ROCHE INC. • NUTLEY 10 • N. J.

Thephorin®
brand of phenindamine

Ointment

'Roche'

*Shelmire, B, *Postgrad. Med.*, 4:443, 1948.

The Bulletin of The New York Academy of Medicine, Vol. 26, No. 4, Published by The New York Academy of Medicine, 2 East 103 Street, New York 29, N. Y. Entered as second-class matter, February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Subscription, Domestic and Foreign copies, $5.00. Single copies, 50c.

Abstract from Gastroenterology
Vol. 13, No. 4, October 1949

A METHOD OF IMPROVING FUNCTION OF THE BOWEL

J. ARNOLD BARGEN, M.D.,
Division of Medicine, Mayo Clinic, Rochester, Minnesota

Constipation, probably the commonest of physical complaints, may be caused by several factors, singly or combined: *1.* nervous fatigue and nervous tension; *2.* improper intake of fluid; *3.* improper dietary habits; *4.* failure to heed the call to stool; *5.* lack of exercise, and *6.* excessive use of laxatives.

It would seem logical that correction of constipation lies in the suitable adjustment of these factors.

Any diet for relief of constipation must supply material which has limited absorption in the small intestines and which adds bulk in the colon, i.e., fruits and vegetables. Daily fluid intake, from 2.5 to 3.5 liters, is highly important. Since many people find it difficult to eat enough dietary bulk, the trend recently has been toward hydrophilous colloids.

A search was made for such a colloid, for oral use, which has little or no effect in the stomach and small intestines. Methylcellulose, appropriately prepared as Cellothyl tablets, seems to answer these criteria.

A large number of patients received 4 tablets every 4 hours, with subsequent relief of constipation. These patients had no ordinary form of constipation; they had taken quantities, or as some said, "barrels of laxatives." In the following cases of obstinate constipation of long duration, a striking change for the better followed the use of this preparation, as part of a program of general medical care:

RESULTS OF TREATMENT

Case 1. Woman, age 57.—Obstinate constipation since early childhood. *After treatment:* Complete relief. She continued to pass normal, soft formed stools.

Case 2. Nun, age 69.—Obstinate constipation of lifelong duration. *After treatment:* In about a week . . . soft stools.

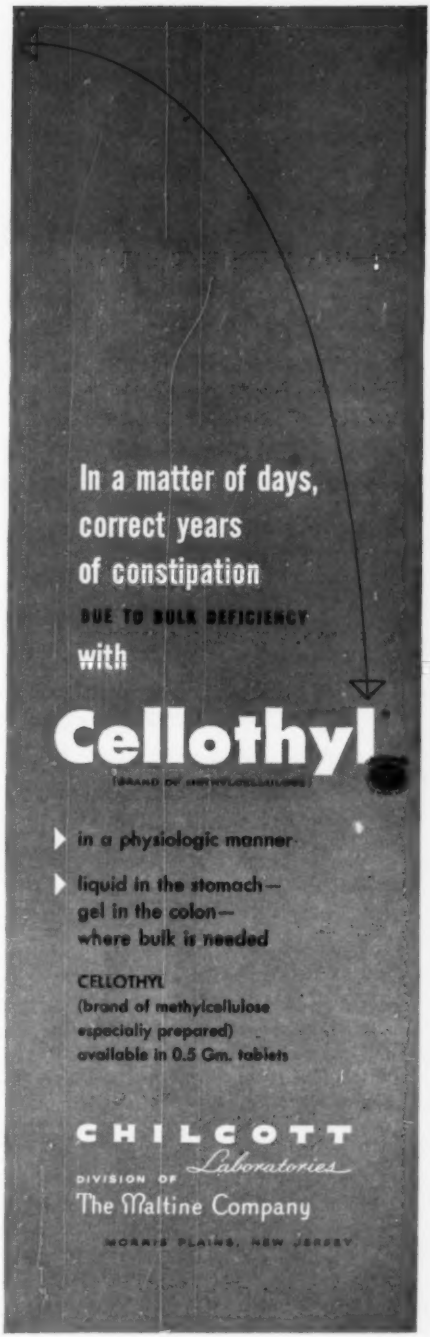
Case 3. Man, age 44.—Constipated many years; severe diabetes. *After treatment:* Normal stools at the end of one week.

Case 4. Woman, age 62.—Very difficult evacuation after carcinoma removal. *After treatment:* She passed her stools without discomfort.

Case 5. Woman, age 19.—Obstinate constipation; she had taken a laxative almost daily since early childhood. *After treatment:* At the end of two weeks she was passing stools daily.

COMMENT

Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared (Cellothyl). It represents a valuable addition to the well-ordered program of medical care.



in hypercholesterolemia

safe and effective reduction
of elevated blood cholesterol
with lipotropic therapy

Clinical and experimental observations indicate that lipotropic factors [choline, methionine and inositol] . . . prevent or mitigate the deposition of cholesterol in the vascular walls of rabbits and chickens and seem to exert a decholesterolizing effect on atheromatous deposits in man, chickens and rabbits.

These findings suggest the therapeutic possibilities of lipotropic Methischol in the prevention and possible treatment of atherosclerosis.

methischol®

Suggested daily therapeutic dose of
3 tablespoonsful or 9 capsules contains:

Choline Dihydrogen Citrate (*Choline . . . 1 Gm.*)*	*2.5 Gm.*
dl-Methionine	*1.0 Gm.*
Inositol	*0.75 Gm.*
Liver Fractions from	*36.0 Gm. liver*
**present in syrup as 1.15 Gm. choline chloride*	

methischol

Supplied in bottles of 100, 250, 500 and 1000 capsules, and 16 oz. and one gallon syrup.

combines major lipotropic agents
for specific therapy in reparable liver damage . . . cirrhosis,
fat infiltration, functional impairment,
toxic hepatitis, infectious hepatitis.

write for samples and literature

u. s. vitamin corporation
casimir funk laboratories, inc. (affiliate)
250 east 43rd st., new york 17, n. y.

THE CLINICAL USE OF ACTH

PROCEEDINGS OF THE FIRST

Clinical ACTH

CONFERENCE

Edited by John R. Mote, M.D.

624 Pages **414 Illustrations** **$5.50**

Ready March 27

These reports have not appeared in print before

THIS BOOK IS

1

The first volume on Clinical use of ACTH to date.

2

A compendium of basic knowledge on adrenal gland stimulation with ACTH in the human being for researchman and practitioner.

3

The *one* book today that can keep you from becoming lost in future developments of ACTH and many areas of medical research.

The First Clinical ACTH Conference, held in Chicago last fall under the auspices of Armour & Co., presented the overall factual picture of adrenal cortical function in normal human beings and patients ill with various disease syndromes.

Here is a complete report of that unique conference . . . the first of its kind ever held.

The purpose of this volume, speeded in preparation and now on press, is to give you, *without delay*, all that was reported and discussed.

SEND FOR YOUR COPY TODAY

The Blakiston Company
1012 Walnut Street
Philadelphia 5, Pa.

THE BLAKISTON COMPANY, 1012 Walnut St., Phila. 5, Pa.
Please send me a copy of Proceedings of the First Clinical ACTH Conference:
☐ charge my account; ☐ my check is enclosed.
It is understood that you will credit my account in full with the book if I wish to return it within 10 days.

Name..... *Address*.....

City..... *Zone*..... *State*.....

NYAM 4-50

FOR

diabetic control

AS INDIVIDUAL AS A FINGERPRINT

The administration of Protamine Zinc Insulin is a cornerstone in the treatment of practically all diabetics because of its slow but prolonged effect. Unmodified Insulin is employed either as a supplement or as an alternative whenever a quick and short but powerful action is required. In emergencies and during diabetic complications, the rapidly acting preparation is especially indicated.

Mixtures of the two preparations provide an intermediate "adjustable" effect. No single Insulin preparation is indicated for all diabetics. The treatment of each diabetic is an individual problem—as individual as a fingerprint.

for rapid effect

Iletin (Insulin, Lilly), U-40 and U-80, containing 40 and 80 units per cc. respectively.

Iletin (Insulin, Lilly) made from zinc-Insulin crystals, U-40 and U-80, containing 40 and 80 units per cc. respectively.

for prolonged effect

Protamine, Zinc & Iletin (Insulin, Lilly)—Protamine Zinc Insulin, Lilly—in vials containing 400 and 800 units, labeled 40 and 80 units per cc. respectively.

for intermediate effect

Suitable mixtures of Iletin (Insulin, Lilly) and Protamine, Zinc & Iletin (Insulin, Lilly).

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

SECOND SERIES APRIL 1950 VOL. 26, NO. 4

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

PRESENT STATUS OF CORTISONE AND ACTH

Effects of Cortisone and ACTH in Rheumatoid Arthritis 206
R. H. Freyberg

The Effect of Cortisone and ACTH on Rheumatic Fever 212
Currier McEwen, Joseph J. Bunim, Janet S. Baldwin, Ann G. Kuttner, S. Baer Appel, Alfred J. Kaltman

Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin . . . 229
George Baehr and Louis J. Soffer

The Use of ACTH and Cortisone in Neoplastic Disease 235
O. H. Pearson, L. P. Eliel and T. R. Talbot, Jr.

Physiology of the Pituitary-Adrenal System . . . 240
Jane A. Russell

The Effect of ACTH and Cortisone on Connective Tissue 251
Charles Ragan, Edward L. Howes, Charles M. Plotz, Karl Meyer, J. Wallace Blunt and Raffaelo Lattes

The Relationship of Adrenal Cortical Activity to Immune Responses 255
Edward E. Fischel

Clinical Research Meeting: *Abstracts* 261

Recent Accessions to the Library 285

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

OFFICERS AND STAFF OF THE ACADEMY

1950

President

BENJAMIN P. WATSON

Vice-Presidents

ALLEN O. WHIPPLE — ASA L. LINCOLN — WILLIAM C. WHITE

Treasurer

SHEPARD KRECH

Recording Secretary

ALEXANDER T. MARTIN

Trustees

GEORGE BAEHR
FRANK B. BERRY
HENRY W. CAVE
ARTHUR F. CHACE
BRADLEY L. COLEY
CONDICT W. CUTLER, JR.
*SHEPARD KRECH
*ALEXANDER T. MARTIN
SETH M. MILLIKEN
HAROLD R. MIXSELL
PAUL REZNIKOFF
*BENJAMIN P. WATSON
ORRIN S. WIGHTMAN

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary
The Chairmen of Standing Committees

Director

HOWARD REID CRAIG

Librarian

JANET DOE

Librarian Emeritus

ARCHIBALD MALLOCH

Executive Secretary
Public Health Relations Committee

E. H. L. CORWIN

Executive Secretary
Committee on Medical Education

MAHLON ASHFORD

Executive Secretary
Committee on Medical Information

IAGO GALDSTON

Legal Counsel

JOHN W. DAVIS, ESQ.

Library Consultants: B. W. WEINBERGER, CURT PROSKAUER

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman* — MAHLON ASHFORD, *Secretary*

DAVID P. BARR — JANET DOE — ROBERT F. LOEB
WILLIAM DOCK — JOHN G. KIDD — WALTER W. PALMER

* Ex-officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

APRIL 1950

PRESENT STATUS OF CORTISONE AND ACTH*

A Symposium

Chairman: ROBERT F. LOEB

Rheumatoid arthritis—RICHARD H. FREYBERG

Rheumatic fever—CURRIER MCEWEN

Lupus erythematosus—GEORGE BAEHR

Neoplastic disease—OLAF H. PEARSON

Metabolic effects—JANE RUSSELL

Effects on connective tissues—CHARLES A. RAGAN

Immune responses—EDWARD E. FISCHEL

* Presented at a Special Meeting of The New York Academy of Medicine, January 12, 1950. Arranged by the Committee on Medical Education.

EFFECTS OF CORTISONE AND ACTH IN RHEUMATOID ARTHRITIS

R. H. FREYBERG

From Cornell University Medical College and the Hospital for Special Surgery, New York, N. Y.

FROM information made available by Dr. James Carlisle of Merck & Co., and by Dr. John R. Mote of Armour Laboratories, it is estimated that in America up to January 1, 1950, Cortisone has been studied in approximately 160 patients with chronic rheumatic disease, and ACTH in about 175 cases. The majority of these patients had rheumatoid arthritis. Since only nine reports of *clinical* experiences with these hormones in rheumatoid arthritis have been published, much of this discussion is based upon the experience of the author and his co-workers,* and upon visits, conferences and reports not yet published.

There is practically uniform experience that rheumatoid arthritis in its various manifestations is quickly and greatly improved when Cortisone or ACTH is administered. With Cortisone a definite pattern of improvement is the rule: First, there is great reduction of stiffness (non-articular) which allows easier and greater range of joint motion, even of the inflamed joints; second, there is reduction often to complete loss of pain at the joints and in non-articular connective tissue; third, progressive decrease in the joint inflammation occurs; articular tenderness is usually the last sign to abate. The time required for these changes to be completed varies from a few days in early stages of the disease to several weeks in older and more severe arthritis. In early cases complete remission usually occurs with disappearance of all abnormal physical signs; in cases of longer standing, some swelling, and effusion may persist although all symptoms frequently subside. Destructive changes of cartilage and bone, ankylosis, ligament calcification remain unchanged. Subcutaneous nodules, bursitis, tenosynovitis and other non-articular features of the disease improve or vanish concurrent with improvement in the arthritis. While these rheumatic abnormalities are improving there

* These investigations were supported by a grant from the Masonic Foundation for Medical Research and Human Welfare and by the Fund for Research in Rheumatic Diseases (Hospital for Special Surgery).

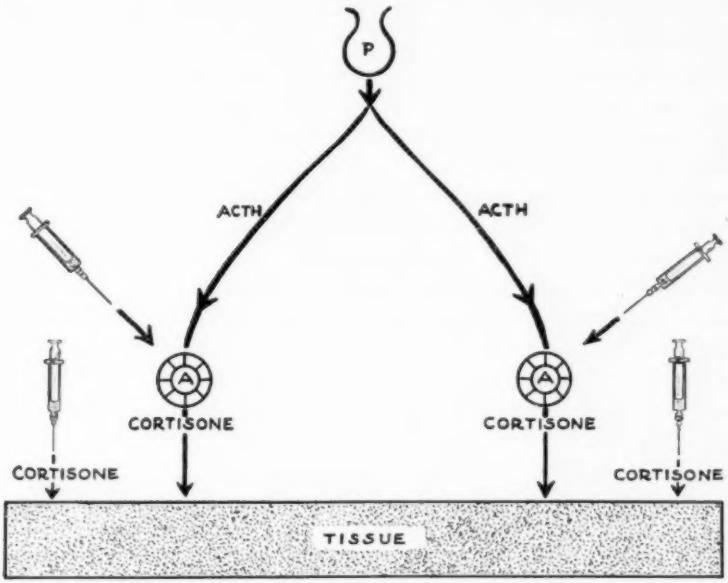


Figure 1—Diagramatic sketch showing the stimulation of the adrenals by adrenocorticotropic hormone from anterior pituitary. Note that effectiveness of ACTH depends upon elaboration of Cortisone which has its effect on the tissues. Similar results are obtained if ACTH is injected to stimulate the adrenal cortices or if Cortisone is injected directly into the tissues.

is comparable improvement in appetite, food consumption, weight, strength and general sense of well-being. Laboratory abnormalities change toward or to normal. A small amount of arthritis may appear for a few days during Cortisone administration but it is indeed minor. On cessation of Cortisone relapse usually occurs; the speed and degree of relapse vary unpredictably under different circumstances.

Juvenile rheumatoid arthritis (Still's disease) and rheumatoid spondylitis respond in all ways similar to classical rheumatoid arthritis. Up to this time we have observed these benefits in six cases of rheumatoid spondylitis. In patients with psoriasis and arthritis (three in the author's group) both conditions improve.

The three predominant attributes which characterize Cortisone are: 1) dependability, 2) speed of action, and 3) the high order of benefit effected.

Potent ACTH (Armour's product has been used in almost all reported studies to date) effects the same dramatic changes seen with Cortisone. Variations, in benefit (usually small) that have been observed between the two hormones can be explained entirely upon differences of amounts of cortico-sterone added to the organism. It must be emphasized that when Cortisone is injected only one cortico-sterone is being added to the human organism and its dose can be regulated at will, whereas the effectiveness of ACTH depends upon the patient's adrenal response to stimulation (Figure 1) so that in addition to a variable dose of ACTH there may also be a variable capacity or degree of cortical response. Although infrequent there have been instances of adrenal response inadequate to effect good results.[1,2] Also there have been instances in which, while continuing doses of ACTH which effected good initial cortical stimulation and clinical benefit, there was progressively less adrenal response as shown by less eosinopenia and relapse in the arthritis. Because ACTH functions through adrenal stimulation and because *all* cortical functions are stimulated, its use may be more complicated than is that of Cortisone.

The manner of action of these hormones is not known. The large amounts required suggest that the connective tissue needs to be flooded with Cortisone—a sort of mass action effect. The speed of response strongly suggests that the benefit is obtained at the tissue level through beneficially altered enzyme-system function; other possibilities include change in antigen-antibody relationship, or tissue permeability. The basic cause of the inflammation and other pathologic changes remains unaltered, directly, by Cortisone, as shown by the relapse following cessation of the hormone; moreover precisely the same joints again become inflamed and nodules, effusions, etc., reappear similar to the pre-hormone conditions. Complications include undesired metabolic or hormone effects which may have "toxic" importance. Some of these will be amplified by others on the panel. In patients with rheumatoid arthritis, edema from sodium retention, potassium depletion, partial hypercortico-adrenalism (facies of Cushing's syndrome, acneiform eruption, hypertrichosis without hypertension and usually without glycosuria), irregular menstruation, hypomenorrhea, temporary amenorrhea with symptoms of menopause, occasional increases in basal metabolism, diabetic carbohydrate metabolism, insomnia, unexplained tachycardia, excitability and mental depression have been observed.[2,3,4]

Occasional complications have been severe,[4] but in our experience with 17 patients who received Cortisone and 16, who received ACTH, no serious complications have been encountered and some of these patients received hormone over long periods, as long as 160, 150, 145 and 120 days. We have had no problem of diabetes, of major nervous or mental changes, and only mild endocrine complications (mild rounding of the face, fuzzy hair growth and irregular menses). Edema responded promptly or could be prevented by restricted sodium intake and the use of ammonium chloride or mercurial diuretic. As reported by others,[3] in our experience all complications or undesired effects have been completely reversible. There is decidedly greater chance for complications in females due to their more complex gonadal functions, and we have seen greater tendencies for endocrine complications in females in the pre-menopausal age. In three male patients who received Cortisone for 160, 145 and 120 days no side reactions occurred and excellent benefit was maintained.

Another set of problems surrounds the dose and schedule of administration. To accomplish remission with Cortisone acetate in adults with rheumatoid arthritis we have found, as did Hench and co-workers[3] and most others, that approximately 100 mgm. daily is required for a period. Divided doses seem to have no advantage over single daily injections. After remission has been accomplished we have found repeatedly that 100 mgm. three times weekly (Monday, Wednesday and Friday) maintain most or all of the benefit for long periods. Some patients with rheumatoid arthritis and spondylitis have been kept in good remission by this plan for 60 to 100 days, as long as this plan has been observed to date. Boland[5] has reported maintenance of good results with 50 mgm. of Cortisone acetate daily. In one of our patients with rheumatoid spondylitis 100 mgm. three times weekly, on Monday, Wednesday and Friday, maintained benefit; when 50 mgm. were given daily, the arthritis worsened; when 100 mgm. were given on three successive days at the first of each week, during the non-treatment days significant worsening occurred, and when 100 mgm. were again given on alternating days maintenance of good remission again obtained. Hench[6] has reported that in some patients intermittent treatment, periods of daily injection separated by periods of several weeks rest from treatment, has given good results in several patients with less relapse after each period of injections. Many more studies are needed to determine best

methods of administration of this hormone over long periods.

There is some question whether complete clinical remission with return to normal erythrocyte sedimentation rate is preferred in stubborn cases if large doses of hormone are required for long periods. It may be better to maintain a good but not complete remission, using less hormone. We have done this in a few patients with satisfaction to the patient and physician. There should be less chance for complications in this plan. It is closer to what Hench has referred to as "coöperating with, rather than taking over completely" the function of the adrenals.[6]

Administration of ACTH is quite different from that of Cortisone. Here the object is to get effective stimulation of the adrenal cortices and experience has shown this is accomplished better by injections of hormone in smaller doses 4 times daily rather than from the entire daily dose given in one injection. The dose of ACTH should be regulated according to the eosinophil response (or other dependable laboratory tests of cortical stimulation) and by clinical results. ACTH dosage has varied more than Cortisone. After 25 mgm. of ACTH (*Armour standard*) 4 times on first day, doses of 10 or 15 mgm. 4 times daily have usually given good remissions, which can thereafter often be maintained for varying periods with smaller amounts. Warning is given that different batches of ACTH have different potency, that mgm. dosage of different lots cannot be compared, that all doses must refer to a biologic standard.

In children, our small experience suggests that dosage of these hormones is not a factor of body size, but depends more upon severity of disease. It has also suggested that to get good antirheumatic effects as much may be needed as in an adult, and that the metabolic and endocrine complications may be greater in the child because of the larger ratio between hormone dose and body size.

Combinations of two or more hormones and of a hormone and enzymes are being investigated. Our results with combined use of adenosine triphosphate and Cortisone or ACTH have been no better than obtained with the hormones alone.

Many substances chemically similar to Cortisone are being studied as possible substitutes. We have made clinical tests with Compound S, progesterone, 17-hydroxy progesterone, Δ^5 pregnenolone, acetoxy pregnenolone, testosterone and 6 other steroids. None have been found beneficial as we used them. These studies are continuing. There is sug-

gestion that if Cortisone be administered for long periods adrenal-cortical atrophy may result, or that adrenal hypertrophy and atrophy of the anterior pituitary may follow prolonged ACTH administration. Whether such changes occur, and if so, their significance and prevention or compensation are further problems requiring investigation. The possible development of undesirable immune reactions, particularly from the protein structure of ACTH, and of allergy from both hormone preparations pose other problems.

All of these unanswered questions should be fully appreciated and many need solution before these hormones can be considered for practical therapy. But also it should be appreciated that the knowledge of pituitary-adrenal hormone relationships to rheumatic disease is the greatest advance in this field of medicine. Never before have such potentialities for the understanding and controlling these diseases existed. I cannot agree with the pessimism occasionally encountered regarding the clinical future. Indeed, there is an inescapable challenge to chemical and medical science to pursue these investigations until there is understanding of rheumatic diseases, and until there are dependable means of treatment.

REFERENCES

1. Thorn, C. W., Bayles, T. B., Massel, B. F., Forsham, P. H., Hill, S. R., Jr., Smith, S., III and Warren, J. E. Studies on the relation of pituitary-adrenal function to rheumatic disease, *New England J. Med.*, 1949, *241*:529.
2. Elkinton, J. R., Hunt, A. D., Jr., Godfrey, L., McCrory, W. W., Rogerson, A. G., and Stokes, J., Jr. Effects of pituitary adrenocorticotropic hormone (ACTH) therapy, *J.A.M.A.*, 1949, *141*: 1273.
3. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. Effect of a hormone of the adrenal cortex (17-hydroxy - 11 - dehydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis: preliminary report, *Proc. Staff Meet., Mayo Clin.*, 1949, *24*:181.
4. Ragan, C., Grokoest, A. W., and Boots, R. H. Effect of adrenocorticotropic hormone (ACTH) on rheumatoid arthritis, *Am. J. Med.*, 1949, *7*:741.
5. Boland, E. W. and Headley, N. E. Effects of cortisone acetate on rheumatoid arthritis, *J.A.M.A.*, 1949, *141*:301.
6. Hench, P. S. Endocrine relationships to rheumatoid arthritis, Address, New York Acad. Med., Jan. 5, 1950.

THE EFFECT OF CORTISONE AND ACTH ON RHEUMATIC FEVER**

CURRIER MCEWEN, JOSEPH J. BUNIM, JANET S. BALDWIN, ANN G. KUTTNER, S. BAER APPEL* AND ALFRED J. KALTMAN

From the Departments of Medicine and Pediatrics and the Study Group on Rheumatic Diseases, New York University College of Medicine, and the Children's Medical Service, Bellevue Hospital, New York, New York.

IN May, 1949, only a month after their initial report on the effect of cortisone and ACTH on rheumatoid arthritis,[1] Hench, Kendall and their co-authors made a preliminary report on the effects of these hormones in three patients with rheumatic fever.[2] All three were in their first or early attacks and all were in the acute phase of the disease. The response of fever, polyarthritis and erythrocyte sedimentation rate was striking. The effect on carditis was much less easy to evaluate and Hench and his associates were careful to avoid drawing conclusions regarding possible benefit to this manifestation of rheumatic fever.

Subsequent experience has amply confirmed the effect on fever, polyarthritis and the general toxicity of the disease but, in the opinion of the writers, judgment must still be reserved regarding carditis. The purpose of this presentation is to summarize current information regarding the effects of cortisone† and ACTH† on various manifestations of rheumatic fever and to report three illustrative cases studied on the Children's Medical Service of Bellevue Hospital. In one patient ACTH was given alone. In two, cortisone was administered first and ACTH was given later after an intervening period without medication. The therapeutic response and metabolic effects observed were essentially the same with both drugs. No conclusions are drawn at this time as to the comparative effects of different or equivalent doses of the two hormones. The observations on these patients with rheumatic

The Study Group on Rheumatic Diseases is supported by a grant from the Masonic Foundation for Medical Research and Human Welfare. Parts of this investigation were aided by grants from the Helen Hay Whitney Foundation and the New York Heart Association.

* Masonic Foundation Fellow.

** Read in modified form at The New York Academy of Medicine, January 12, 1950 as part of a Symposium on cortisone and ACTH.

† The authors are indebted to Drs. James M. Carlisle, Medical Director of Merck and Co., Inc., Rahway, New Jersey and John R. Mote, Medical Director of The Armour Laboratories, Chicago, Illinois, for the cortisone and ACTH used in these investigations.

fever have been aided by experience gained in the study of eleven additional patients with rheumatoid arthritis or scleroderma who received cortisone or ACTH or both.

Effects on Features Other Than Carditis

As already noted, there has been ample confirmation of the response of fever, polyarthritis, rheumatic toxicity and erythrocyte sedimentation rate to adequate amounts of cortisone and ACTH. The response to both these hormones appears to be similar and it is probable that what is said in the succeeding paragraphs about one may be assumed to be true also of the other.

Fever: The response of fever is striking, the temperature of all patients reported to date reaching normal in from one to five days. This is well illustrated by patient C. M. (Case 1, Fig. 1) whose temperature fell from 106.8° two hours before therapy was begun to 98.6 16 hours following the start of ACTH. The fall in fever apparently is not specific for rheumatic fever for it occurs also in unrelated diseases such as acute leukemia, pneumonia and tuberculosis.[3]

Polyarthritis: This manifestation responds dramatically also. In reported cases all evidences of inflammation of the joints disappeared in two to six days[2-5] except in the case of one of Hench's patients,[2] who lost all acute inflammation in three days but in whom mild metatarsal tenderness persisted for eight days more. Only one patient in the present report had joint involvement (patient C. M. Case 1, Fig. 1) and this disappeared completely after 48 hours.

Rheumatic Toxicity: This unsatisfactory expression is used here to mean the malaise, prostration and mental clouding so common in patients acutely ill with rheumatic fever. These symptoms have subsided rapidly at approximately the same rate as the fever. Probably distinct from this return to a normal sense of well-being is a decided euphoria experienced by some patients receiving either cortisone or ACTH.

Associated with the sense of well-being there has been distinct increase in appetite and gain in weight. This gain must be differentiated from that due to salt and water retention which commonly occurs in patients receiving cortisone or ACTH.

Subcutaneous Nodules: None of the three patients reported here had subcutaneous nodules. However, three of nine patients observed

by Massell[3, 5] had nodules which became much smaller or disappeared entirely in two to three weeks.

Miscellaneous Manifestations: None of the patients studied by the authors had rashes or chorea. Pleuritis with effusion appeared in one patient (Case 2) two days before therapy and cleared on the fourth day of cortisone administration.

Hematological Changes: The *erythrocyte sedimentation rate* responds strikingly but less rapidly than fever and polyarthritis. Usually there is little or no change for the first four or five days but then the rate falls steadily to reach normal in ten days to three weeks following the administration of hormone.

The total *white blood cell count* in rheumatic fever has not been observed to follow a definite pattern although the trend is toward a return to normal. In some patients the fall is rapid as in patient A. B. (Case 2, Fig. 2) while in others leukocytosis continues for some time (Fig. 1) or may increase. The leukocyte response is probably influenced by the effect of cortisone and ACTH *per se* on hematopoietic tissue.[6]

Definite increases in *hemoglobin* and *erythrocyte counts* have been observed. An impressive increase in the hemoglobin and a somewhat less striking increase in erythrocytes occurred in Patient C. M. (Case 1, Fig. 1) treated early in the first attack of rheumatic fever. Two days before the administration of ACTH the hemoglobin was 9.3 gms. per 100 cc. of blood. By the end of the fourth week of therapy it had increased to 12.8 gms. without the aid of antianemic drugs, and the erythrocyte count had increased from 2,880,000 to 3,840,000. In patient A. B. (Case 2), who was studied three months after the onset of his first rheumatic attack, hemoglobin increased from 9 gms. four days before treatment to 11.2 gms. at the end of the fourth week of ACTH. In contrast, patient M. B. (Case 3) who received these hormones after nine months of continuous, chronic, active carditis, showed no significant increase in hemoglobin with either cortisone or ACTH. Whether these differences in response are related to the different duration of rheumatic activity in the three patients cannot, of course, be stated on such limited experience.

Changes in Blood Proteins: A slight increase in serum albumin and fall in serum globulin has been reported in rheumatic fever following the administration of cortisone.[2] This observation was confirmed in the three patients of the present series. Other blood proteins studied

included fibrinogen, gamma globulin and the "C" reactive protein.[7] The changes in the three patients are shown in Tables I, II and III. The fibrinogen concentration in the blood fell as cortisone or ACTH was administered and, in the one patient for whom data were available (Case 3), rose again after the hormones were discontinued. There was a fairly good correlation between the fibrinogen level and the erythrocyte sedimentation rate, both following a parallel course. The serum gamma globulin was increased in two patients before therapy and became normal with treatment. The parallelism observed between the erythrocyte sedimentation rate and the fibrinogen concentration was not observed with the gamma globulin. The "C" reactive protein fell to normal as the patients improved.

Changes in Antistreptolysin-O Titers: The titers of antistreptolysin-O are recorded also in Tables I, II, and III. In the two patients who showed definite improvement the titers fell progressively. Whether this fall was directly due to cortisone and ACTH or reflected naturally occurring changes cannot be said. However, the latter is suggested by the results of Fischel, reported in the final paper of this symposium.[8] He did not observe significant changes in the titer of various antibodies following the administration of ACTH.

Electrolyte Metabolism: Changes in sodium, potassium, chlorides, CO_2 combining power, uric acid, non-protein nitrogen, the uric acid/creatinine ratio, and glucose followed the patterns recorded for normal individuals and patients with other diseases receiving cortisone and ACTH.[4, 9-12] The data for some of these are recorded in Figures 1, 2 and 3.

Effects on Carditis

Striking as the effects of cortisone and ACTH are on fever, polyarthritis and general toxicity of rheumatic fever, equally dramatic results can be induced much more simply and inexpensively by adequate doses of salicylates. This is not true of anemia, subcutaneous nodules or erythrocyte sedimentation rate, but these are not in themselves of serious concern to the patient. Hence, cortisone and ACTH will mark an important advance in the treatment of rheumatic fever primarily if they prove to benefit the major manifestation of the disease which is not significantly altered by salicylates, namely, carditis.

Unfortunately, it is not easy to draw conclusions about a disease

like rheumatic fever, which is subject to "spontaneous" changes for better or worse. Pericardial friction rubs have been reported to disappear in two to three days following administration of cortisone or ACTH;[2,3,5] and this was so in the three patients reported here although electrocardiographic evidence of pericarditis persisted longer. However, both friction rubs and electrocardiographic changes of rheumatic pericarditis may be evanescent without any therapy. The same is true of changes in atrioventricular conduction time.

At present, also, it is difficult to draw conclusions from such reports as have been made regarding changes in cardiac murmurs. In one patient reported by Hench et al,[2] a diastolic murmur suggestive of aortic insufficiency was heard for the first time on the 16th day of cortisone therapy and was observed intermittently for the succeeding two weeks, after which it disappeared. Massell[3,4] reported the disappearance of a basal diastolic murmur in one patient and of apical systolic and diastolic murmurs in another receiving ACTH. In the three patients reported here, long established murmurs have not been altered significantly (Cases 2 and 3) but a murmur of recent origin has regressed (Case 1).

Heart rate has tended to parallel temperature. In early cases of rheumatic fever it has returned to normal in three to five days[2,3,5] as illustrated in Case 1. In patients with long standing and severe active rheumatic heart disease, fall in ventricular rate has been slow (Cases 2 and 3). Hench et al[2] reported that, in early cases, the return of ventricular rate to normal may be followed by bradycardia of 40 to 60 beats per minute lasting for several weeks. This was observed also in patient C. M. (Case 1) whose rate fell to 58 per minute temporarily.

Finally, the results of cortisone and ACTH administration to patients with congestive heart failure in the presence of carditis have, in the opinion of the writers, been equivocal. This is illustrated in Cases 2 and 3.

Case Reports

Case 1—Patient C.M., a Polish girl nine years of age, entered the hospital on the sixth day of illness. Family history was negative for rheumatic diseases. She gave a history of normal childhood. Previous illnesses included measles at six years and infrequent colds. There was no history of tonsillitis, muscular pains or rheumatic fever. During

1948 and 1949 she had experienced occasional episodes characterized by a macular, pruritic rash over the neck, face and body, associated with fever of 103° to 104° and vomiting. These attacks were attributed by her parents to the ingestion of tomatoes and apples. None of these attacks lasted more than three days. The most recent attack had occurred one week prior to her present illness.

On 22 December 1949, six days before admission to the hospital, the patient complained of frontal headache and malaise. The following day she experienced anorexia and fever of 103°. On 24 December the left ankle became painful, followed next day by involvement of the right ankle, both knees and the right fifth finger. Her physician gave her aspirin and sulfathiazol in small doses for three days with little effect, and because of continued symptoms referred her to Bellevue Hospital on 28 December with a diagnosis of rheumatic fever.

On admission to the Childrens Medical Service the temperature was 104°, and pulse 140 and respirations 36 per minute. She was pale and appeared acutely ill. Over the back there was a fading rash which suggested erythema marginatum. No subcutaneous nodules were found. Severe pain was elicited by the slightest motion of body or extremities. Redness and swelling were noted in all proximal interphalangeal and metacarpophalangeal joints of both hands and all metatarsophalangeal joints of both feet. The knees and ankles were also painful, red and swollen. The heart sounds were "overactive" and the rhythm was that of regular sinus tachycardia. No gallop or friction rub was heard, but there was a loud, harsh, low-pitched systolic murmur at the apex transmitted to the left as far as the posterior axillary line. No other murmurs were heard and there was no thrill. Lungs were clear. Liver and spleen could not be palpated but there was slight tenderness in both upper quadrants of the abdomen.

Course: The course is illustrated in Fig. 1. Temperature continued to be high, the polyarthritis remained severe and on 30 December a pericardial friction rub appeared. On that afternoon the temperature rose to 106.8° but, after an iced bed bath, had fallen to 103° two hours later at 3:00 P.M. when ACTH was started. The dose was 15 mg. intramuscularly every six hours. An hourly temperature record revealed no fall in fever for the first ten hours, but temperature then descended rapidly to 98.6° in the next six hours. Thus temperature fell to normal in sixteen hours after a total of only 45 mg. of ACTH. By

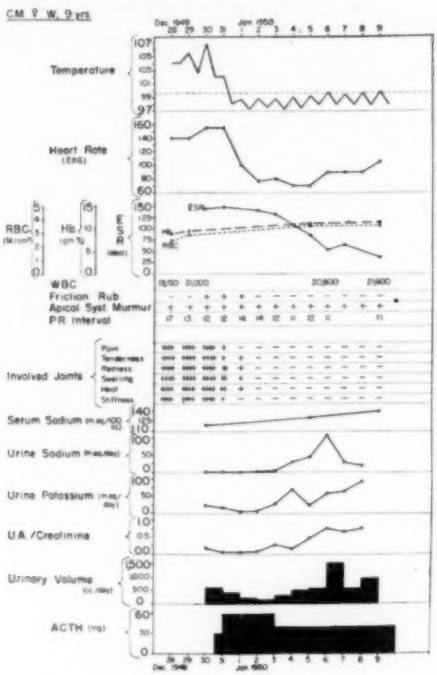


Figure 1—Clinical Course in Patient C.M. (Case 1.)

RBC=Red blood cells in millions per.
Hb=Hemoglobin ESR=Erythrocyte sedimentation rate (Westergren).
WBC=Total leukocytes per.
U.A./Creatinine=Urinary uric acid/Creatinine ratio.

that time joint pain was already much less severe, and articular symptoms and signs had disappeared entirely by the third day after the start of ACTH. On that day also the pericardial friction rub could no longer be heard although electrocardiographic evidence of pericarditis was more persistent. Elevation of the S-T segment was observed for nine days and minimal T-wave changes for three weeks.

The subsequent course was very favorable. Rectal temperature did not rise above 99.8°. Pulse varied between 70 and 100 per minute but it was soon apparent that the higher rates were psychogenic, and sleep-

TABLE I—SEDIMENTATION RATES, BLOOD PROTEINS AND ANTISTREPTOLYSIN O TITERS OF PATIENT C. M. (CASE 1).

		Amount ACTH Daily Mgm.	*ESR (Westergren)*	*Fibrinogen Mgm%*	*Gamma Globulin Kunkel U./100 cc.*	*"C" Reactive Protein Immed.*	*After 2 hrs.*	*After 24 hrs.*	*Anti-streptolysin O Units*
Days Before ACTH	2					3+	3+	4+	
	1		145	1350	29.0	3+	4+	4+	400
Days On ACTH	4	60	131	750	25.5	2+	2+	2+	400
	6	40	86	400		—	+	+	
	8	40	65	400					
	10	40	36	350	23.0				
	12	25	21	300					
	13	25	23	220	12.8	—	—	—	
	17	40	20	210					
	19	40	14		11.0	—	—	—	200
	21	40	20	250					
	24	20	11.5	350					
	26	20	13	220	9.5				
	28	20	11			±	±	+	
	31	10	11	270					

ing pulse rate was 58 to 80 per minute. The erythrocyte sedimentation rate changed little for the first four days. Thereafter it fell gradually to reach normal on the twelfth day after the start of ACTH. The total white blood cell count remained high for four weeks and did not reach normal until 3 February by which date the dose of ACTH had been reduced to 10 mg. daily. The erythrocyte count and hemoglobin rose steadily in spite of frequent bleedings for laboratory purposes. As shown in Fig. 1, serum sodium, the urinary excretion of sodium and potassium, and the uric acid/creatinine ratio all rose considerably beginning the third to fourth day after the start of ACTH. Conversely, urinary output decreased at first but rose subsequently. By 11 January 1950 the patient's face began to become rounder and she gradually developed a definite "moon face." On 30 January an eruption appeared on the forehead. This consisted of pin-head sized yellowish-pink acuminate lesions with absence of oiliness and comedones. Subsequent to the period shown in Fig. 1, there was sufficient water retention to cause edema. Because of this ACTH was discontinued 24 to 48 hours on two occasions with resultant prompt diuresis. The systolic

murmur rapidly lost its harsh quality and became less loud. Fluoroscopic examination on 27 January revealed only doubtful evidence of transverse enlargement of the heart and no abnormalities of contour. The daily amount of ACTH was gradually decreased and was stopped altogether on 13 February. As this report goes to press on 6 March, 1950 she shows no evidence of continuing rheumatic activity and appears to be progressing most satisfactorily although a systolic murmur persists at the apex.

Case 2—Patient A.B., a white boy of eight, was admitted to the hospital on the sixty-fourth day of his first attack of rheumatic fever. Two years previously he had had a brief episode of pain and stiffness of the right knee but there was no tenderness or swelling and the symptoms cleared spontaneously. Two of his mother's first cousins died of rheumatic fever and his father was reported to have rheumatic heart disease.

The onset was on 1 June 1949 when the patient had an upper respiratory infection with high fever followed several days later by pain in the left foot and fleeting pains in the shoulder, neck and lower spine with no objective changes. On 9 June the sedimentation rate was 32 mm but an electrocardiogram and a teleroentgenogram were normal. On 6 July a gallop was heard, and also systolic and diastolic murmurs at the apex. On 30 July a pericardial friction rub appeared and the temperature rose to 103°. The patient had become mildly dyspneic and had five bouts of epistaxis up to the date of admission on 3 August.

When he entered the hospital the temperature was 102.2°, the pulse rate 140 and respiratory rate 30. The patient was obese, pale and moderately dyspneic. The neck veins were distended. The apical impulse was palpable in the anterior axillary line. The rhythm was regular and the rate 140. At the apex, systolic and diastolic murmurs were heard. The heart sounds were distant and obscured by a loud, pericardial friction rub which was heard for three inches on either side of the mid-sternal line. The liver margin was palpable two finger-breadths below the right costal margin. The venous pressure was 230 mm of water. On fluoroscopic examination the heart was markedly enlarged. The silhouette was consistent with dilatation and enlargement of the heart and pericardial effusion.

Figure 2 illustrates the clinical course and presents some of the laboratory data collected. On the day before cortisone therapy was

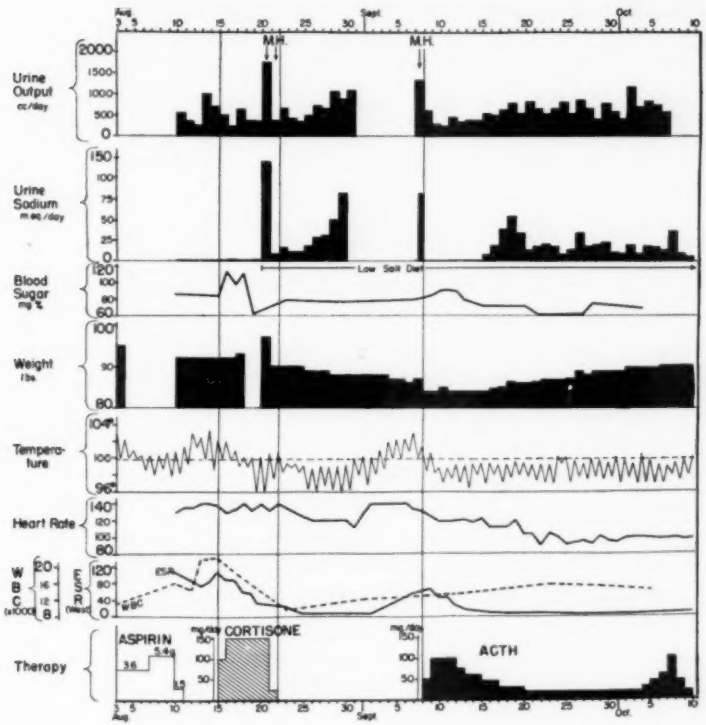


Figure 2—Clinical Course in Patient A.B. (Case 2.)
M.H.=Mercuhydrin. Others as in Fig. 1.

started the friction rub disappeared. With cortisone the fever, leukocytosis and sedimentation rate rapidly returned to normal but the tachycardia and character of the heart sounds were unaffected. On the fifth day of treatment (20 August) the patient's congestive failure increased; cyanosis and severer dyspnea appeared and his condition became critical. Cortisone was discontinued and mercuhydrin, given intramuscularly, was followed by diuresis and a striking increase in urinary sodium excretion which up to this time had been zero both before and during steroid administration. The fever and sedimentation rate remained normal for ten days after cortisone was withheld and

TABLE II—SEDIMENTATION RATES, BLOOD PROTEINS AND ANTI-STREPTOLYSIN O TITERS OF PATIENT A.B. (CASE 2).

			ESR (Westergren)	*Gamma Globulin Kunkel U./100 cc.*	*"C" Reactive Protein Immed.*	*After 2 hrs.*	*After 24 hrs.*	*Anti-streptolysin O Units*
Days		11		15.5				
Before		3	88					
Cortisone		1	107	18.5	2+	3+	3+	400
Days on		2	87					
Cortisone		4	55					
Days After								
Cortisone		1	20		—	+	±?	317
Stopped.								
Days								
Before	6	10	7	8.8				
ACTH	1	15	52	8.0	2+	3+	3+	159
Days		2	45					
On		4	27					
ACTH		6	15					
		8	6	9.6				
		11	3	8.5				
		13	1		—	—	—	125
		18	3	6.7				
		25	5	6.7				
Days		1	8	6.2				
After		8	7	10.2				83
ACTH		15	7	7.0				
Stopped		22	7	6.8	—	—	—	—
		29	7	7.9	—	—	—	—
		36	3	6.1				<100

clinically he was considerably improved. Then fever and sedimentation rate began to rise and the patient's condition became worse and failure increased. From 1 September through 6 September no determinations had been made of the urinary sodium excreted. On 7 September this was again found to be zero and mercuhydrin was given. During the following eight hours 80 milliequivalents of sodium were excreted. Treatment with ACTH was begun the next day. Sodium retention occurred during the first seven days of therapy but with no ill effects. The temperature and sedimentation rate returned to normal, body weight increased and the general condition was improved. On the twelfth day of ACTH therapy the heart rate had fallen below 100 for the first time; but this was at the end of the 16th week of the disease.

The heart continued to sound overactive and the rate remained labile for four weeks after ACTH was discontinued or 5½ months after the onset of rheumatic fever. The heart had decreased somewhat in size but remained enlarged and both the apical systolic and diastolic murmurs persisted. The electrocardiogram showed no significant changes. At the time of discharge to a convalescent home on 11 January the patient was still thought to have low-grade active carditis.

Case 3—Patient M.B., a 9 year old girl, was admitted to the hospital with long standing active rheumatic carditis and congestive heart failure which did not yield to digitalis therapy. At age 6 she had a brief episode of pain in the knee and fever. At age 8 (May, 1948) she had both polyarthritis and chorea. At that time the diagnosis of heart disease was made and the patient was kept in bed for three months. She was then ambulatory for four months and in January, 1949 was ordered back to bed because of active rheumatic heart disease. This state persisted until her admission to Bellevue Hospital on 24 September 1949. The child had been receiving digitalis since 15 July because of signs of failure.

On admission she was seriously ill, thin, pale, cyanotic and dyspneic. Respirations were 50 per minute, the heart rate 140, the blood pressure 110/65 and the temperature 101.4°. The neck veins were distended. The heart was enlarged to right and left with heaving apical impulse. A loud systolic murmur and a long, low-pitched, early and mid-diastolic rumbling murmur were heard at the apex. A pericardial friction rub was also present. Fine rales were audible at both bases posteriorly. The liver edge was tender and felt 4 to 5 cms. below the costal margin. There was no peripheral edema and no subcutaneous nodules. Fluoroscopic examination revealed marked generalized cardiac enlargement with weak pulsations. The clinical course and some of the laboratory data are charted in Figures 3 a and b.

Cortisone produced no striking improvement and did not obviate the need for digitalis and mercuhydrin. The heart rate remained rapid and there was no clear evidence that the carditis had subsided although temperature and erythrocyte sedimentation rate fell. Five weeks after cortisone was stopped the patient's condition became worse. Dyspnea, tachypnea, orthopnea, pallor and "toxicity" were accentuated. ACTH therapy was started. This time the sedimentation rate which was 40 mm failed to come down although the temperature fell sharply. The

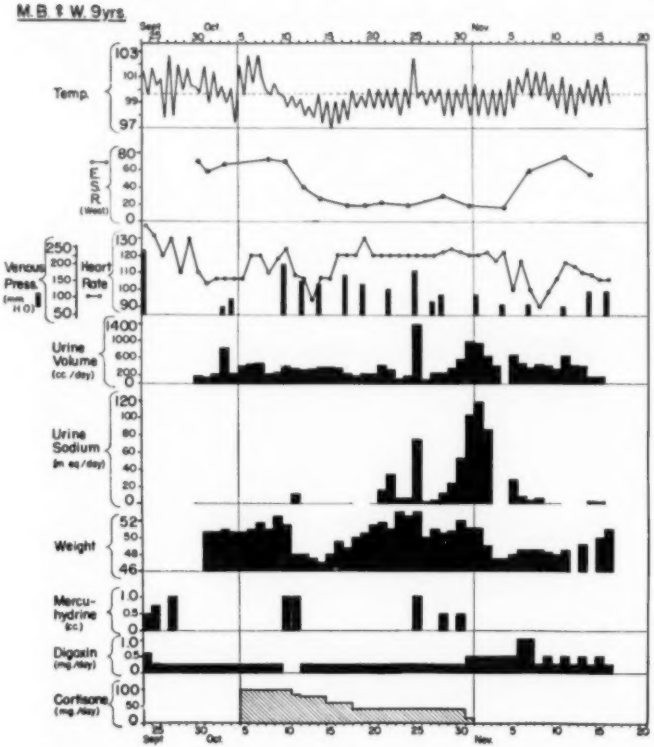


Fig. 3a

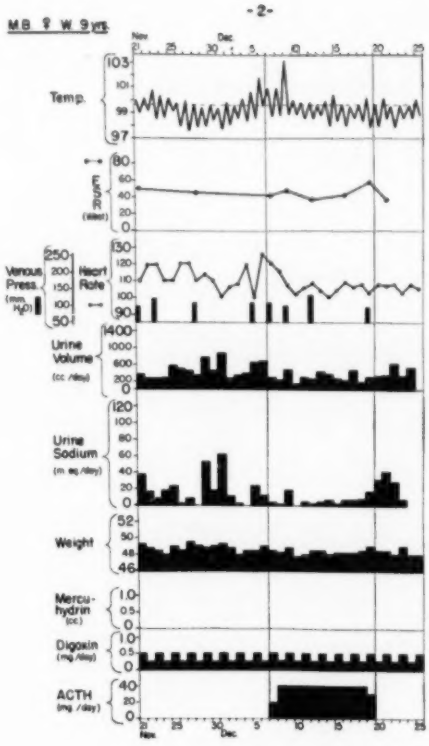


Fig. 3b

Figures 3a and 3b—Clinical Course in Patient M.M. (Case 3)

TABLE III—SEDIMENTATION RATES, BLOOD PROTEINS AND ANTI-STREPTOLYSIN O TITERS OF PATIENT M.B. (CASE 3).

		Esr Wester-gren	*Fibrinogen Mgm%*	*Gamma Globulin Kunkel U./100 cc.*	*"C" Reactive Protein Immed.*	*After 2 hrs.*	*After 24 hrs.*	*Anti-streptolysin O Units*
Days Before Cortisone	5	70		12.8	2+	3+	3+	
	1	70	500					317
Days on Cortisone	2	73		12.5				
	6	70		12.8				
	8	40	352		—	—	2+	
	10	27						
	13	14	249	11.5	—	—	+	
	17	16						
	20	14		10.3	—	+	2+?	
	27	18		14.0	—	—	+	200
Days After Cortisone Stopped	4	16	374					
	7	60	554	12.8				
	14	55	470	15.5				200
	21	50		16.8				
Days Before ACTH	10	28	45		16.3	—	+	+	200
	1	37	42		16.5	2+	3+	3+	200
Days on ACTH	2		48	510		2+	3+	3+	
	5		38	380	14.7	+	+	2+	
	9		42						
	12		58		15.2				200
Days After ACTH Stopped	2		36						
	10		46	570		—	+	2+	
	24					—	2+	3+	300
	38					±	+	3+	

patient improved from a critical state to one of "smouldering" activity and as this is written, in February 1950, she remains in that condition.

UNTOWARD EFFECTS

In all probability patients with rheumatic fever who receive cortisone or ACTH are subject to the same undesirable side effects as are patients with other diseases. These include transient hypertension, glycosuria, mental disturbances, salt and water retention, hypokalemia, a peculiar facial eruption, and rounding of the facial contours or other

features of Cushing's syndrome.[3] Of the three patients reported here one (Case 1) developed a "moon face" and facial eruption on the 13th and 32nd days respectively of ACTH administration. All three patients showed salt and water retention which, in the case of the two children in congestive failure, was associated with an exaggeration of the symptoms and signs of failure. Among 11 additional patients with other diseases observed by the authors, one adult with rheumatoid arthritis receiving ACTH developed transient hypertension of 170/104 as compared with 108/68 before therapy, and a child with Still's disease had marked but transient glycosuria on both cortisone and ACTH.[3] Several had mild edema resulting from salt retention.

Discussion

In spite of the limited experience to date with cortisone and ACTH in the management of rheumatic fever, the beneficial effects on fever, "rheumatic toxicity" and polyarthritis seem already amply established. The effects on erythrocyte sedimentation rate, anemia and subcutaneous nodules also appear to be unquestionable. There is some evidence to suggest that carditis is benefited too but, in the opinion of the authors, a definite decision is not yet warranted regarding the latter.

If one may draw an analogy from the course of events in patients with rheumatoid arthritis treated with cortisone and ACTH, one would expect rheumatic carditis to be benefited. In rheumatoid arthritis the granulomatous lesions in the synovial tissues as well as the subcutaneous nodules improve most strikingly. In rheumatic fever also the subcutaneous granulomas disappear under the influence of these hormones[3, 5] and it is reasonable to expect, therefore, that the same may be true of the myocardial granulomas.

Unfortunately, more direct evidence of benefit to carditis is difficult to evaluate. As has been pointed out, rheumatic pericardial friction rubs and atrioventricular conduction defects have cleared rapidly in a number of patients receiving cortisone or ACTH; but similar changes can occur with equal rapidity without therapy. In the hope of obtaining an early answer to the question the authors selected for study two children with active carditis and severe congestive heart failure (Cases 2 and 3). It was anticipated that hormone therapy would lessen myocardial inflammation and that the resultant improvement in myocardial function would be reflected in a decrease or disappearance of heart

failure. To the contrary, however, signs and symptoms of heart failure increased, probably as the result of increased salt and water retention. The temperature and erythrocyte sedimentation rate fell and, after diuresis induced by mercurials, the patients' general condition was improved; but it was not possible to conclude with assurance just what role the hormones had played. It seems probable that a final decision as to the value of cortisone and ACTH in rheumatic carditis will be reached only after painstaking analysis of end results of cardiac damage in a statistically significant number of patients treated early in the disease.

It is, perhaps, worth commenting on the possible relationship between the differences in benefit induced by cortisone and ACTH in the three patients reported here and the duration of disease. Patient C.M., who received ACTH on the sixth day of rheumatic fever, made striking improvement; whereas patient A.B., treated on the 76th day of disease, showed less striking benefit, and patient M.B., who had had continuously active carditis for nine months, showed the least of all. Further experience may prove these results to be merely coincidental but they invite speculation.

It appears to be clear that the real importance of cortisone and ACTH in rheumatic fever will depend on whether or not they benefit that major manifestation of the disease—carditis—which is not significantly affected by salicylates. There is sufficient evidence to warrant the hope that they do, but further experience is required for final judgment.

Summary

Cortisone or ACTH was administered to three children with rheumatic fever and rheumatic heart disease. The earlier observations of Hench and others regarding the striking benefit to the fever, polyarthritis and anemia of the disease was confirmed. The erythrocyte sedimentation rate and the fibrinogen concentration in the blood fell in a roughly parallel fashion as cortisone or ACTH was administered. The serum gamma globulin, which was increased in two patients before therapy, became normal during treatment. The "C" reactive protein also fell to normal as the patients improved as did the antistreptolysin O titer in two of the patients. Changes in sodium, potassium, chlorides, CO_2 combining power, uric acid, non-protein nitrogen, uric acid crea-

tinine ratio, and glucose followed the patterns observed in normal individuals and patients with other diseases receiving cortisone and ACTH.

The effect on rheumatic carditis was less definite. Two patients with active carditis of 2½ and 9 months duration showed no immediate improvement in heart failure. One patient treated on the sixth day of rheumatic fever showed striking improvement of carditis and apparently was completely well following 44 days of treatment. Sufficient evidence has accumulated to warrant the hope that cortisone and ACTH do benefit rheumatic carditis but further experience is required for final judgment.

REFERENCES

1. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: *The Effect of a Hormone of the Adrenal Cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis.* Proc. of the Staff Meetings of the Mayo Clinic *24*:181-197 (April 13) 1949.
2. Hench, P. S., Slocumb, C. H., Barnes, A. R., Smith, H. L., Polley, H. F., and Kendall, E. C.: *The Effects of the Adrenal Cortical Hormone 17-hydroxy-11-dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever: Preliminary Report.* Proc. of the Staff Meetings of the Mayo Clinic *24*:277-301 (May 25) 1949.
3. The Proceedings of the First ACTH Conference, Armour and Company, Chicago, Illinois.
4. Thorn, G. W., Bayles, T. B., Massell, B. F., Forsham, P. H., Hill, S. R., Smith, S., and Warren, J. E.: *Medical Progress: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease.* New England J. Med. *241*:14: 529-537 1949.
5. Massell, B. F.: Personal Communication.
6. Dougherty, T. F. and White, A.: *Influence of Hormones on Lymphoid Tissue Structure and Function. The Role of the Pituitary Adrenotrophic Hormone in the Regulation of the Lymphocytes and Other Cellular Elements of the Blood.* Endocrinology *35*:1:1-14 1944.
7. Tillett, W. S. and Francis, T. Jr.: *Serological Reactions in Pneumonia with Non-protein Somatic Fraction of Pneumococcus.* J. Exp. Med. *52*:561-571 1930. MacLeod, C. M. and Avery, O. T.: *Occurrence During Acute Infections of Protein not Normally present in Blood; Isolation and Properties of Reactive Protein.* J. Exp. Med. *73*:183-190 1941.
8. Fischel, F. E. *Immune responses to cortisone and* ACTH, Bull. New York Acad. Med., 1950, *26*:255.
9. Conn, J. W., Lovis, L. H. and Johnson, M. W.: *Metabolism of Uric Acid, Glutathione and Nitrogen, and Excretion of "11-oxysteroids" and 17-ketosteroids during induction of Diabetes in Man with Pituitary Adrenocorticotropic Hormone.* J. Lab. Clin. & Med., *34*:255 1949.
10. Ingle, D. J.: *Some Studies on the Role of the Adrenal Cortex in Organic Metabolism.* Annls. of the N. Y. Acad. of Sci. *50*:6:576-595 1949.
11. Pincus, G.: *Adrenal Cortex Function in Stress.* Annls. of the N. Y. Acad. of Sci. *50*:6:635-645 1949.
12. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., Bergner, G. E., and Hills, A. G.: *Clinical Studies in Addison's Disease.* Annls. of the N. Y. Acad. of Sci. *50*:6:646-656 1949.

TREATMENT OF DISSEMINATED LUPUS ERYTHEMATOSUS WITH CORTISONE AND ADRENOCORTICOTROPIN*

GEORGE BAEHR AND LOUIS J. SOFFER

Mount Sinai Hospital, New York

As Hench and Kendall have reported, disseminated lupus erythematosus can be arrested by cortisone and ACTH. This was to be anticipated from our own observation that this disease, which occurs predominantly in females (95 per cent of all cases), often enters a remission during a period of gestation.

The following report is a brief summary of the observations of a group of investigators at the Mount Sinai Hospital, New York. Our experience is now based upon the treatment of nine patients with various forms of collagen disease, of whom five were typical examples of disseminated lupus erythematosus. Of the five, four were females and one a boy of thirteen. Only patients who were extremely ill and appeared to be on the verge of death were selected for therapy because the drugs were in such scarce supply. The required daily therapeutic dose of cortisone for severe cases of long standing proved to be 150 to 200 milligrams a day in four divided doses; of ACTH about 100 milligrams a day, also administered intramuscularly in four divided doses.

Before treatment was begun, the patients with disseminated lupus erythematosus were tested for response of their adrenal cortex to stimulation by adrenocorticotropic hormone. Intramuscular injection of 50 milligrams was promptly followed in each case by a normal response, as evidenced by a significant drop in circulating eosinophiles and by increased urinary excretion of the neutral 17-ketosteroids and 11-oxygenated steroids.

Patients in extreme exacerbations of the disease, some who were almost moribund, responded to adequate cortisone or ACTH therapy within 48 hours with a feeling of well-being, improvement in strength,

* Supported by grants from the New York Foundation and the Division of Research Grants and Fellowships, National Institutes of Health U.S.P.H.S.
Part of the ACTH was contributed by the Armour Laboratories.

and amelioration of arthralgia. The temperature usually falls to normal by the fourth day of treatment; gallop rhythm and tachypnea, if present, subside; mouth lesions heal; pain and swelling of the joints disappear; and any previous evidences of pleuritis and pericarditis thereafter rapidly vanish. Within ten days after the beginning of adequate therapy, the characteristic erythema disappears, except perhaps for some residual pigmentation of the previously affected areas, and the patients appear well on the road to convalescence.

After the disease had been arrested by cortisone and the patients appeared to be clinically well, usually after two or more weeks of therapy at maximum doses, the amount was gradually reduced every three or four days until a maintenance level was determined. The daily maintenance dose required to hold the gain was found to lie between 50 and 100 milligrams. Reduction below that amount usually resulted within three or four days in a recrudescence of the fever and a return of arthralgia, serous membrane involvement, extreme weakness, and other manifestations of the illness. Complete withdrawal of the drug resulted within a few days in prompt recurrence of the disease so that it became necessary to reinstitute therapy in full doses to prevent jeopardizing the patient's life.

These experiences soon led us, even on the first patients, to substitute ACTH for cortisone as soon as the minimum maintenance requirement for cortisone had been determined. It was our impression that the continued use of large doses of cortisone had partially suppressed adrenal cortical function and, therefore, after the disease had been controlled clinically by cortisone, the patients required a reactivation of adrenal cortical function by ACTH stimulation if relapse was to be prevented. Replacing the maintenance dose of cortisone with an equivalent amount of ACTH (75 to 100 milligrams a day in four divided doses for four or five days), the daily amount was gradually reduced by slow stages during the succeeding four to six weeks until the patient's own adrenals had assumed the full load. In this manner the patients were slowly weaned of their need for ACTH.

Although the treated patients lost all manifestations of the disease and appeared to have recovered clinically, their illness must be regarded as only in remission. In all our patients in whom the disease has been arrested by cortisone-ACTH therapy, the leukopenia persists, the erythrocyte sedimentation rate remains accelerated, and the so-

called "L.E." cells can still be found in heparinized bone marrow or in the buffy coat of heparinized blood. Recurrences can therefore be anticipated subsequently in most of these patients, which will require repetition of the treatment.

It is important to emphasize that the administration of these hormonal preparations in the required doses is accompanied by serious hazards. Within a week after the onset of therapy, a rapid gain in weight may occur, due in large part to increase in body water and to associated disturbances in the distribution of blood electrolytes. Simultaneously, both the systolic and diastolic blood pressures may tend to rise significantly. This combination of events may suddenly induce congestive heart failure and acute pulmonary edema. Such serious complications are most apt to occur within the second week of treatment in patients with severe lupus erythematosus, for their heart muscle is already severely injured, as indicated frequently by gallop rhythm, and their pericardium is often the site of an intense serositis.

As in Cushing's disease, a shift in blood electrolytes to the cells may result in alkalosis. The use of mercurial diuretics to combat congestive heart failure may, in our experience, accentuate this tendency. In one of our patients who developed repeated attacks of acute pulmonary edema both while under cortisone therapy and ACTH therapy, the repeated intramuscular injection at these critical times of 2 cc. of mercuhydrin as a life-saving measure was followed by a rise of the CO_2 combining power of the blood plasma to 102 volumes per cent and a drop in blood chlorides to 79 milliequivalents per liter. Simultaneously, the serum potassium dropped to 1.9 milliequivalents per liter, although the serum sodium level remained normal. It became urgently necessary to administer hypertonic potassium chloride intravenously to correct the alkalosis and the threatening hypopotassiumemia, either of which could have been fatal.

In an endeavor to avoid the retention of sodium and of water and thereby prevent congestive heart failure, a boy of thirteen in a severe exacerbation of disseminated lupus erythematosus was kept on a low-salt diet containing 8.5 milliequivalents of sodium per day for a week before as well as during the entire period of cortisone therapy. During the first eight days of hormonal therapy, his body weight remained constant. Meanwhile, the disease responded characteristically to the hormone by decline in the temperature to normal by the fourth day, in-

creased strength, appetite, and felling of well-being, disappearance of arthralgias and signs of pleuritis, and gradual clearing of the butterfly-shaped facial erythema between the fifth and twelfth days after beginning treatment. The systolic and diastolic pressures remained at previously normal levels. The absence of weight gain during the first eight days was unlike our previous experience with patients treated with large doses of cortisone while on an unrestricted diet containing salt.

In spite of the low-salt intake (8.5 milliequivalents of sodium a day), the boy gained one pound on the ninth day and two and a half pounds on the tenth. It was then noted that his liver had become enormously swollen, the tender edge being palpable at the level of the umbilicus, and the neck veins were distended due to an increase of venous pressure to 16 cm. It was feared that he was on the verge of congestive failure. He was therefore immediately given an intramuscular injection of 1 cc. of mercuhydrin and the cortisone therapy was discontinued. The injection of mercuhydrin was followed by a good water diuresis of two liters within the next 24 hours and a drop of three pounds in body weight. However, the water diuresis during this 24-hour period was not accompanied by an increased urinary output of sodium, although there did occur a moderate increase in the urinary excretion of potassium. The sodium content of the 24-hour urine was practically identical with the daily sodium output during the previous period of salt restriction. On the day after the water diuresis, the CO_2 combining power of the blood plasma had risen to 74 volumes per cent, although at that moment the sodium and potassium content of the plasma was within the normal range, and the chlorides fell from 100 to 96 milliequivalents per liter.

Equally interesting was the observation of a marked sodium diuresis in this boy on the day following the water diuresis, the 24-hour output of sodium rising suddenly from 15 to 100 milliequivalents. As this occurred on the second day following discontinuance of cortisone therapy, it can be ascribed, at least in part, to release on that day of the sodium-retaining effect of cortisone.

This case demonstrated that: 1) the favorable therapeutic influence of cortisone in disseminated lupus erythematosus is not prevented or adversely affected by a low-salt intake; 2) salt restriction may prevent the elevation in blood pressure which may occur during cortisone therapy and it delays but does not prevent the characteristic increase

in body water; 3) under the conditions of the experiment, water diuresis following the intramuscular administration of a mercurial diuretic may occur without simultaneous sodium diuresis; 4) sodium diuresis following administration of a mercurial diuretic may be prevented or delayed by the inhibitory influence of cortisone.

Among other hazards it must be mentioned that cerebral disturbances were encountered in two patients under treatment with cortisone and ACTH. In one young woman with lupus erythematosus, treatment with cortisone had to be discontinued on the 18th day because of the occurrence of repeated epileptiform convulsive seizures. The electroencephalographic pattern returned to normal within a few days after therapy was terminated. In another woman with lupus erythematosus, cortisone and later ACTH therapy was continued successfully in spite of the development of alternating periods of manic and depressive psychosis. In this instance the hormonal therapy seemed to exaggerate greatly what were probably the patient's psychiatric tendencies.

During the course of therapy with cortisone and with ACTH, we have found the blood proteins of patients with disseminated lupus erythematosus to be influenced favorably. Patients who have been acutely ill with this disease for many months usually show a conspicuous reduction in total blood proteins due to a drop in serum albumin, whereas their serum globulin is usually elevated above normal levels and may exceed the serum albumin. Coburn and Moore determined electrophoretically that the gamma globulin fraction was increased but failed to note that the alpha "A" fraction was also increased, an observation made subsequently by Miriam Reiner of our laboratory. Miss Reiner has demonstrated on our patients that, under the influence of these hormones and simultaneous with improvement in the disease, the serum albumin rises with a coincident increase in total protein, and both the gamma globulin and alpha "A" fractions gradually approach normal values.

Summary

The adrenal cortex of patients with disseminated lupus erythematosus responds normally to ACTH stimulation. It can be stated that cortisone and ACTH are life-saving in disseminated lupus erythematosus, inducing a remission of the disease even when therapy is

begun at a time when patients are critically ill with a serious exacerbation of the disease. They are extremely potent remedies, the use of which is accompanied by serious hazards due to rapid shifts of blood electrolytes between cells and intercellular spaces and increases in total body water sufficient to induce congestive heart failure and pulmonary edema. In some instances the systolic and diastolic blood pressure may be elevated during treatment with large doses. Therapy may induce a disturbance in acid balance sufficient to cause alkalosis. This tendency may be seriously accentuated when mercurial diuretics are administered to combat congestive heart failure, due in part to excessive loss of chlorides. Ordinarily, the sodium and potassium content of the blood of patients under treatment with this hormone remains at normal levels, but under the influence of a mercurial diuretic, potassium may be rapidly lost in the urine at a time when sodium is retained because of the influence of the cortisone. The resulting hypopotassiumemia may place the patient's life in serious jeopardy. It is therefore recommended that these extremely potent hormones should be used at present on patients with disseminated lupus erythematosus only in a hospital equipped with a specially trained staff and with facilities for accurate chemical and physiological measurements.

Finally, it is necessary to emphasize that the dramatic improvement of the disease under therapy, even apparently complete clinical recovery, cannot be interpreted as more than a remission. The condition of these patients must still be regarded as most precarious, for the persistence of leukopenia, accelerated sedimentation rate of the erythrocytes, and the persistence of L.E. cells in the bone marrow or blood indicate that the disease is still active and the unknown cause has not been eliminated.

It would seem from these observations that the administration of large doses of cortisone and ACTH to patients with disseminated lupus erythematosus prevents or arrests the abnormal enzymatic processes in mesenchymal cells initiated by an unknown causative factor. The action of these potent hormonal agents is in this sense non-specific. Hence their wide spectrum of effectiveness in a great variety of disease processes (rheumatoid arthritis, rheumatic fever, disseminated lupus erythematosus, allergies, pemphigus, wound healing, etc.) which have one thing in common, namely, that their various causative factors exert a detrimental influence primarily upon the collagenous or, in a broader sense, the mesenchymal tissues of the body.

THE USE OF ACTH AND CORTISONE IN NEOPLASTIC DISEASE*

O. H. Pearson, L. P. Eliel and T. R. Talbot, Jr.**

From the Division of Clinical Investigation, Sloan-Kettering Institute, and the Department of Medicine, Memorial Hospital

We have previously reported[1] that the administration of ACTH*** or cortisone acetate to patients with lymphoid tumors results in a temporary regression in the size of enlarged lymph nodes and spleens. These observations were made on four patients with chronic lymphatic leukemia, one with follicular lymphosarcoma, and one with Hodgkin's disease. In all of these patients regrowth of tumor masses became manifest within ten days to three months after discontinuing the hormones. Metabolic studies provided evidence that tumor tissue was actually destroyed during treatment. Three patients, two with leukemia and one with lymphosarcoma, have shown a second response to therapy. No obvious effect on tumor growth was obtained with the administration of ACTH to one patient with carcinoma of the prostate and one with carcinoma of the breast.

During the past few months further observations have been made on the use of ACTH and cortisone in patients with acute leukemia and various types of tumors. No definite effect on tumor growth was observed in six patients; one each with carcinoma of the breast, embryonal carcinoma of the testis or adrenal, Ewing's tumor, plasma cell myeloma, rhabdomyosarcoma, and carcinoma of the pancreas.

Five previously untreated patients with acute leukemia have received ACTH. Remissions have occured in all five, three of whom were children and two adults. One of the children had acute lymphatic leukemia; the other four patients acute granulocytic leukemia. ACTH

* These studies were supported by grants from the U. S. Public Health Service, the Office of Naval Research, The Atomic Energy Commission, the Damon Runyon Cancer Research Fund and the American Cancer Society.

** The authors wish to acknowledge assistance in obtaining and selecting patients and helpful advice in carrying out these studies from the following: Drs. C. P. Rhoads, Lloyd F. Craver, Rulon W. Rawson, Konrad Dobriner, Joseph Burchenal, Henry Diamond, David Karnofsky and George Escher. We also wish to acknowledge the technical assistance of Miss Alma Manieri, Mr. Harold Kamen, Miss Mary Beeman and Miss Sylvia Tedesco.

*** The ACTH used in this study was generously supplied through the courtesy of Dr. John R. Mote of the Armour Company.

was given in a dose of 50 mgs daily to children and 100 mgs daily to adults for periods of twenty-four to thirty days. All patients showed symptomatic improvement within the first few days of treatment. There was rapid shrinkage in the size of enlarged lymph nodes and a decrease in the size of enlarged spleens and livers. Bleeding from the nose, urinary tract, and bowel, and purpura in the skin and mucous membranes ceased within the first few days of treatment. All patients developed a voracious appetite during the first week of therapy.

The first signs of improvement in the hematologic picture was an increase in the maturity of the circulating white blood cells, which occurred on the fourth to the sixth day of treatment. Increase in the number of reticulocytes occurred on the fifth to the eleventh day. Maximum reticulocyte responses of 10 to 20 per cent were obtained during the second to third week of therapy. Platelets increased on the ninth to the seventeenth day. In the two adults the initial white cell count was elevated: 28,000 and 92,000. In both patients the white count fell to subnormal levels within two to four days, and then rose slowly to normal levels. The three children had subnormal white counts initially, varying from 650 to 3,200. In all patients the white cell counts rose slowly, reaching normal levels after three to four weeks therapy.

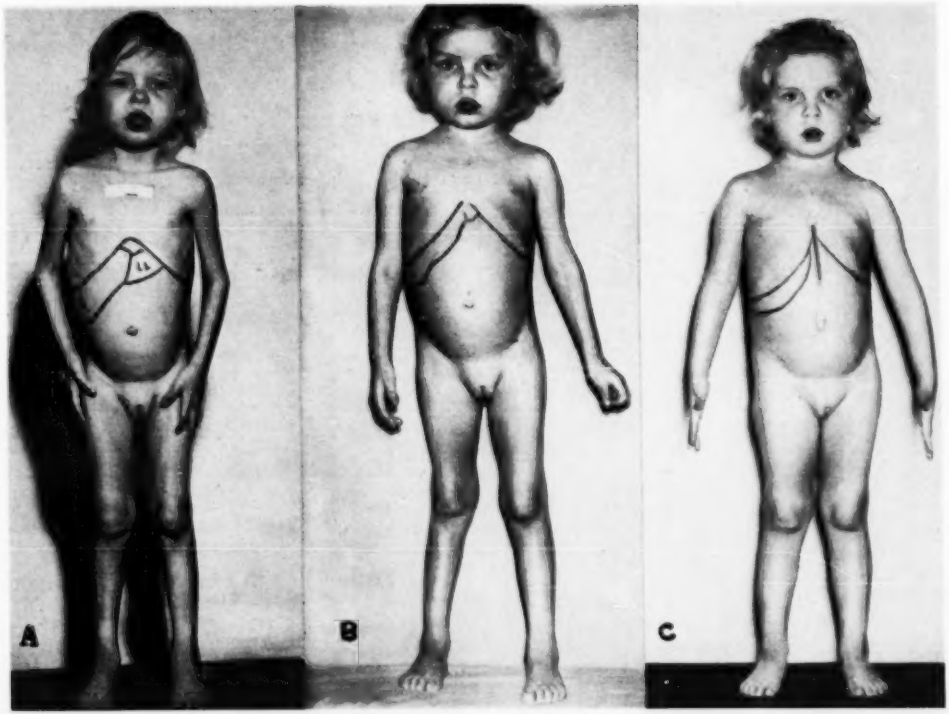
Improvement in the bone marrow was first manifest by an increase in erythropoietic activity, occurring on the fourth to the eighteenth day of treatment. Increased maturity of the myeloid cells occurred on the eleventh to the twenty-first day. In none of the patients has there been a complete disappearance of abnormal cells from the bone marrow or peripheral blood.

One child remains in remission five weeks after stopping ACTH. Another child developed clinical and hematologic relapse three weeks after stopping ACTH. ACTH was again administered with symptomatic improvement. This patient is still receiving treatment. The other three patients continue in remission one to sixteen days after discontinuing therapy.

The clinical and hematologic responses in one patient with acute leukemia who received ACTH are illustrated in Figures 1 and 2.

Two children with acute leukemia previously treated with antifolic substances died two and fifteen days after beginning ACTH therapy. Death in the patient who received ACTH for only forty-eight hours was caused by secondary infection as a contributing factor to

Figure 1. B.P. M.H. no. 97781



11-7-49
A. After two days of ACTH administration

12-13-49
B. Eight days after stopping ACTH

1-6-50
C. One month after stopping ACTH

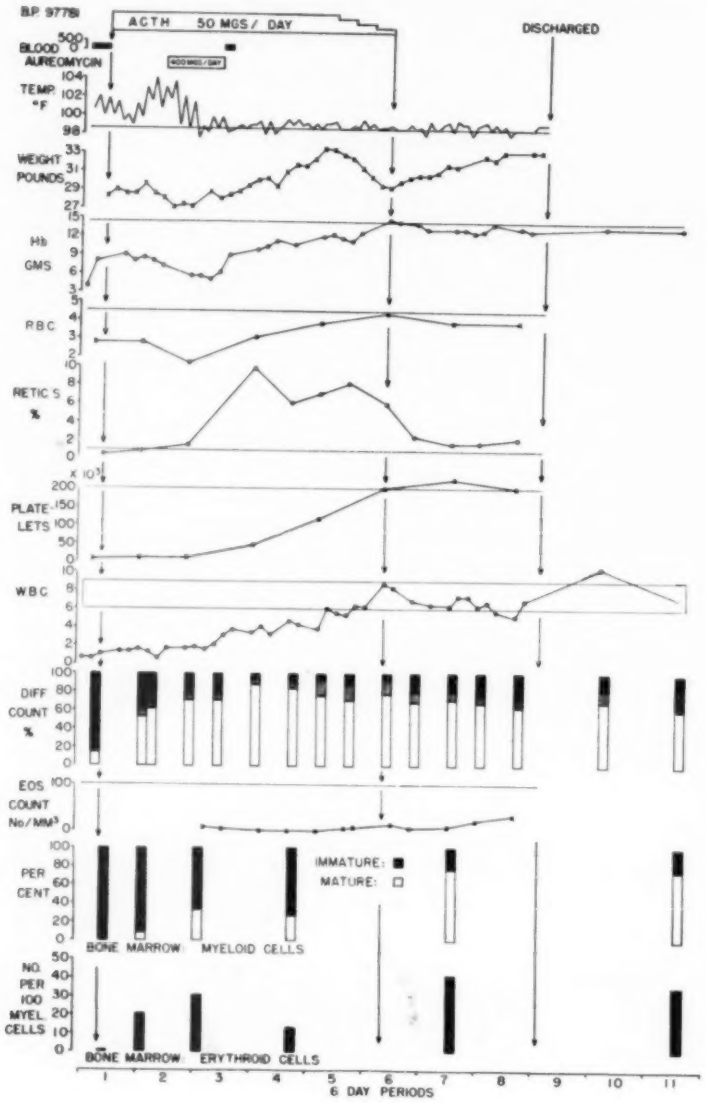


Figure 2

Differential white blood count: black is immature forms, shaded area is lymphocytes, and white area is polymorphonuclear leukocytes.

the leukemia. The second child was critically ill at the time of starting ACTH with generalized edema, pyrexia and bleeding from the nose, gastrointestinal and urinary tracts. There was some clinical improvement during ACTH therapy as manifested by disappearance of fever and some increase in appetite, but there was no evidence of hematologic improvement.

Experience with cortisone in acute leukemia is limited. One child with acute leukemia has shown a good remission with the use of cortisone. Another critically ill child with acute leukemia died forty-eight hours after starting cortisone therapy.

These studies indicate that remissions can be induced in acute leukemia of both children and adults with considerable regularity by the use of ACTH. At the present state of this study, it must be considered that these remissions are both incomplete and temporary.

REFERENCES

1. Pearson, O. H., Eliel, L. P., Rawson, R. W., Dobriner, K. and Rhoads, C. P. ACTH- and cortisone-induced regression of lymphoid tumors in man, *Cancer*, 1949, *2*:943.

PHYSIOLOGY OF THE PITUITARY-ADRENAL SYSTEM

JANE A. RUSSELL

Department of Physiological Chemistry, Yale University, New Haven

It may be said at once that what is known of the actions of adrenal hormones does little to explain the effects seen in the treatment of rheumatic and allergic states with cortisone or ACTH, to which attention has been drawn recently in such dramatic fashion. But there are many points concerning adrenal physiology which bear recalling in connection with possible undesired reactions during treatment with potent steroids; further, I should like to leave you with some idea of the directions in which newer investigations may be proceeding.

First, we may recall the chemical nature of the known adrenal steroids. Some 28 or 30 different steroids have been isolated from adrenal gland tissue, of which 6 or 7 are active in maintaining life in adrenalectomized animals. The structures of these are shown in Fig. 1. There are two important classes of active adrenal steroids, those oxygenated at carbon atom 11 (C-11) and those not. The latter are generally described as of the desoxy type; they are relatively easy (if not simple) to synthesize, but unfortunately they do not possess complete therapeutic powers.

Compound B was the first of the 11-oxygenated forms of which the structure was determined. It was then called corticosterone, and the chemical names of other adrenal steroids, later identified, were referred to this substance. Compound A, differing only in having a keto rather than a hydroxyl group at C-11, is similar in its properties and activities to compound B.

Compound E is the one now known as cortisone. It differs from Compound A by having in addition a hydroxyl at C-17. It was synthesized (from bile salt steroids) a few years ago by the chemists at Merck, a formidable achievement in synthetic chemistry. It is about twice as active in most respects as compound B or A.

Compound F is similar to compound E in having a C-17 hydroxyl

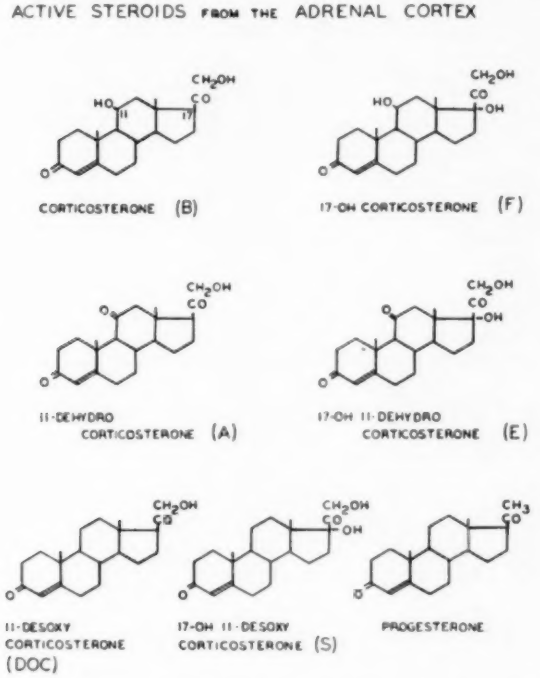


Fig. 1—Steroids isolated from the adrenals which will maintain life in adrenalectomized animals. (Symbols A, B, E and F after Kendall).

and like compound B in the C-11 hydroxyl. Recent work not yet reported in detail appears to indicate that compound F is the principal component of the adrenal steroids as found in the gland and as secreted by it. It is about 50 to 100 per cent more active than cortisone, and 3-4 times as active as compound B or corticosterone; but unfortunately it is still more difficult to make synthetically.

Relative activities of several of the adrenal steroids, as estimated by different methods of testing, are shown in Table I. It may be seen that the approximate ratios of activity mentioned above apply to some of the major functions of the cortical hormones, but not to all. The desoxy type of compound, much less active in the glycogenic and muscle

TABLE I—RELATIVE ACTIVITIES OF SOME ADRENOCORTICAL STEROIDS

Steroid	*Mode of Assay*				
	*Glycogenic effect**	*Muscle work performance**	*Cold protection**	*Growth and Survival**	*Dog maintenance***
17-OH corticosterone (F)	148	192		100	20
17-OH, 11-dehydrocorticosterone (E)	100	100	100	100	
Corticosterone (B)	54	63	9	80	
11-dehydrocorticosterone (A)	48	48	33	60	
11-desoxycorticosterone (DOC)	0	2	8	400	300
Amorphous fraction		10		250	500

* Compared to 17-OH, 11-dehydrocorticosterone. Tested in adrenalectomized rats.
** Tested in adrenalectomized dogs.
(From data of Kuizenga (1944), Pabst *et al* (1947), and Dorfmann (1949).

work tests, is more active in maintaining life. The amorphous fraction consists of as yet unidentified steroids, apparently resembling in action the desoxy compounds.

Physiological effects of the hormones. These may be classified roughly as follows:

a) on salt and water balance and related processes;

b) on organic metabolism (carbohydrate, protein, and fat);

c) on lymphoid and other mesenchymal tissues;

d) on resistance to changes in environment or stress of various types.

No point of action of the hormones common to all these categories is known. One would expect there to be such a process, some single reaction responsible for all the many effects; but if it exists, it has not been identified. As yet the separate types of activity must be discussed individually.

a) *Salt and water balance.* Figure 2 illustrates some of the effects of removal and replacement of hormone in the adrenalectomized dog. These data are taken from a paper of Harrop et al; as you remember, it was Dr. Loeb and his group who first clearly showed similar effects in Addison's disease, now some years ago. Note the large losses of salt and retention of potassium and the reversal with treatment. The elevation in blood NPN which is commonly seen in acute adrenal insufficiency is also shown.

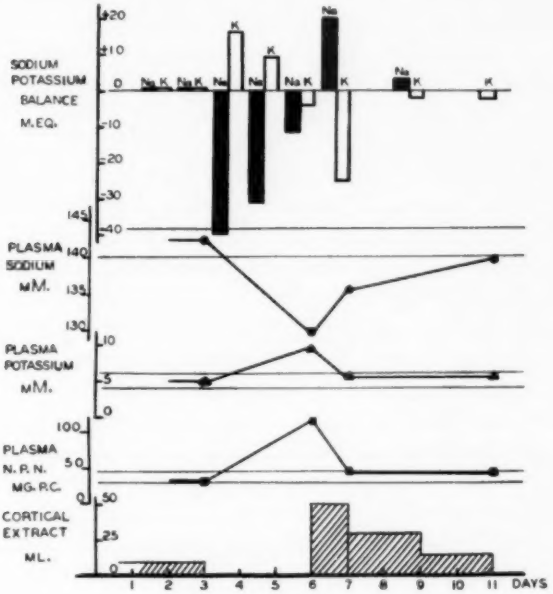


Fig. 2—Effects of withdrawal and replacement of adrenocortical extract in the adrenalectomized dog (after Harrop *et al*, 1936). Constant amounts of food and water were given during the period of observation. Fine lines indicate approximate range of values seen in normal animals.

Besides the action of adrenal hormones on sodium and potassium excretion, the distribution of minerals and water in the tissues is affected, and also the excretion of water. Effects on tissue electrolytes and "permeability" are ill understood. Some recent evidence indicates that the delayed excretion of water and perhaps the loss of salt in adrenal insufficiency may be the result of increased activity of the posterior pituitary anti-diuretic hormone. (The apparent increased activity may be the result of either increased secretion of this substance, diminished destruction of it, or increased sensitivity to it in the adrenal deficient animals.)

Most experimental work indicates that the retention of nitrogen, low blood pressure, etc., seen in acute adrenal insufficiency are primarily

TABLE II—EFFECTS OF ADRENOCORTICAL EXTRACT ON CARBOHYDRATE STORES AND NITROGEN EXCRETION IN NORMAL FASTING RATS*

	Liver Glycogen	*Muscle Glycogen*	*Blood and tissue fluid glucose*	*Total Carbohydrate*	*Nitrogen Excretion (12 hours)*
Untreated Rats	7	253	37	297	54
Cortical extract given hourly	79	260	54	383	81
Increase	72	—	17	89	27

* Fasted 24 hours, with treatment during last 12 hours. All values are in mg. per 100 gm. body weight (from Long et al, 1940).
Note that the ratio of extra carbohydrate to extra nitrogen is 3.3, indicating that the new carbohydrate found could all have come from body protein catabolized during the period.

referable to the loss of body salts and water and the resulting low blood volume and diminished blood flow. This is perhaps not entirely correct, but the fact is that these latter changes may often be prevented largely or entirely by the administration of salt (plus restriction of potassium in some cases). Other indirect effects—by indirect we mean those which can be prevented by salt or other supportive therapy, without hormone—include those on appetite, digestion, and intestinal absorption, and growth in young animals. The assays shown in Table I, which utilize as criteria the effects on survival and growth of young rats and maintenance of life in dogs, seem to measure primarily actions on salt and water balance.

In adrenal insufficiency, the alterations in salt and water balance and consequent derangement in hemodynamics and kidney function are perhaps the most important with respect to *survival*, at least under ordinary conditions. These changes can be entirely prevented by appropriate therapy with quite small amounts of the 11-oxygenated steroids, or with desoxycorticosterone (which has little effect on other than salt metabolism), or often with salt alone, as I have mentioned. Yet animals so treated are far from normal in other respects. In physiological as distinct from pathological terms, these actions of the adrenal hormones on mineral metabolism seem less important than the further functions to be outlined.

In normal individuals it is rather difficult to demonstrate effects of cortical steroids on salt and water metabolism. It appears that the normal

rate of secretion of the hormone is more than adequate to care for ordinary needs in these respects. However, very large amounts of potent steroids may induce retention of sodium, and with it, retention of water as well. Such effects have been seen recently in patients treated with cortisone.

b) *Organic metabolism.* Some of the effects of adrenal hormones on organic metabolism are illustrated in Table II. In normal fasting rats the hormone induces increased excretion of nitrogen and increased deposition of liver glycogen. These are parallel phenomena, and so it has been generally concluded that the action of the hormone is on some phase of gluconeogenesis from body protein. Most of the evidence indicates that the primary site of action is the breakdown of body protein, the gluconeogenesis following as a gesture of economy by the normal fasting animal. This effect on nitrogen balance is perhaps paralleled clinically by the wasting of muscle tissue seen in Cushing's syndrome. Adrenal deficient subjects show little change from the normal in their metabolism in the fed state. In fasting, when normally protein is catabolized at an increased rate and gluconeogenesis is stepped up, the adrenalectomized animal is less able to adapt to the lack of food. The liver glycogen and blood sugar fall, and in some species hypoglycemia is a frequent cause of death.

In fed subjects, there is some evidence also that utilization of carbohydrate is impaired under the influence of excess adrenal hormone. Ingle has found that when rats are force-fed diets high in carbohydrate, glycosuria may be induced by the administration of large amounts of adrenal hormones and also of certain estrogenic steroids. We have observed diminution in the R.Q. and increased deposition of glycogen in acute experiments in rats fed glucose and given cortical extract. The mechanism of this action is not certain, for utilization of carbohydrate may include not only oxidation but also fat formation. This so-called diabetogenic action of adrenal hormones may be one of the untoward effects mentioned earlier, for a mild or incipient diabetes of pancreatic origin may be exacerbated by treatment with adrenal hormones or ACTH.

Adrenal hormones also effect an increase in the excretion of uric acid; the reason is not known, but it may result in part from the dissolution of tissues, such as the lymphoid cells. A purely renal action in uric acid excretion has also been suggested.

An additional function probably metabolic in nature concerns the ability of the muscles to respond to prolonged repeated stimulation. The muscles of adrenalectomized animals cease to react in a short time, but treatment with active steroids restores this ability. This finding is used as a basis of assay of adrenal hormone fractions, as shown in Table I.

In all of these metabolic effects, the C-11 oxygenated steroids are by far the more active, although the desoxy type may not be completely inert.

c) *Lymphoid and mesenchymal tissues.* The effects of cortical hormones on lymphoid and other mesenchymal tissues are relatively recent discoveries. It had been known for many years that many conditions of stress were associated with lymphopenia and involution of lymphoid tissues, but the mediation of adrenal hormones in this phenomenon was not suspected at that time. It is now found that these changes do not occur in adrenalectomized animals subjected to stress, and that they can be reproduced by the administration of cortical hormones or in hypophysectomized animals by ACTH. A diminution in circulating eosinophils, first noted by Thorn and his coworkers, is particularly striking, and this effect is now used as an indicator of adrenal activity in experimental work in man and animals.

Dougherty has recently demonstrated specific effects of the adrenal steroids on subcutaneous mesenchymal tissues, with infiltration of eosinophils and other alterations meaningful to the histo-physiologist. He has suggested that the eosinophils which disappear from the blood are to be found accumulated in tissues of this type.

Another recent observation possibly related to these effects, made by Opsahl, is that the active adrenal steroids have a pronounced inhibitory effect on the "spreading factor" of the skin. This action seems to be due to inhibition of hyalonuridase, an important enzyme which acts upon the ground substances in interstitial spaces. The effect is immediate and may be observed after local application of the cortical steroids.

As in the case of the metabolic effects, so with respect to lymphoid and similar tissues we find that only the C-11 oxygenated adrenal steroids are active.

These matters cannot be discussed further here; but they are mentioned to make the point that the actions of the adrenal hormones on the morphology and presumably on the physiology of the tissues appear

not to be confined to lymphoid cells and eosinophils, but are probably very wide-spread in tissues of mesenchymal origin. The answer to the question of the mechanism of the adrenal hormone activity in rheumatic and allergic reactions may well lie in further study of such phenomenon as have been mentioned.

d) *Resistance to stress.* The fourth category of actions of the adrenal hormones concerns resistance to stress or adaptation to changes in environment. This is not a satisfactory classification to a physiological chemist like myself, for the terms "resistance" and "adaptation" are words which mainly serve to cover our ignorance. What is known is that in adrenal insufficiency, the subject is very sensitive to all kinds of untoward influences—to cold, heat, trauma, infections, toxins, many drugs, hemorrhage, hypersensitivity reactions, among them—and that he can be protected by active adrenal steroids. The C-11 oxygenated steroids are by far the most effective here. The mechanism by which the hormone promotes resistance to stress is unknown. It seems likely that these unknown processes should include as part of their mechanisms some or all of the known types of activity described above, and perhaps others of which we do not yet know.

In most instances it is not possible to induce any additional degree of resistance in normal subjects by the administration of extra hormone. This may be because in these instances, such as trauma, anoxia, and so on, there are other limiting factors in the response of the individual than the amount of adrenal hormone available. This does not mean that some less severe stresses could not be mitigated, if we knew how to measure their effects on the organism, or that other different types of responses could not be improved upon. Indeed, if we consider allergic manifestations or rheumatic reactions (which may be a type of hypersensitivity response) to be peculiar kinds of stress, then we may say that we are enabling the hypersensitive (but apparently otherwise normal) individual to deal with the allergen in better fashion by giving him extra adrenal hormone.

The relationship of the pituitary to the adrenal responses. No mention has been made of ACTH, the adrenocorticotrophic hormone, in discussing the actions of the cortical hormones, because its systemic effects (in animals with intact adrenals) are identical with those of the C-11 oxygenated steroids. You are probably familiar with the intimate physiological relationship between the adrenal and pituitary. In the

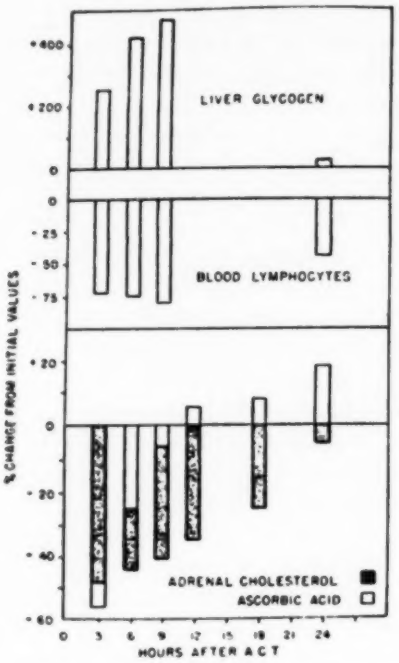


Fig. 3—Parallel effects of a single dose of ACTH on liver glycogen, blood lymphocytes, and adrenal cholesterol and ascorbic acid in the rat (from Long, 1947).

absence of the hypophysis, the adrenal cortex is atrophic. It is probably not entirely without function, since the hypophysectomized animal does not die of adrenal insufficiency; but as we have said, only very small amounts of adrenal hormones are required to maintain life. The hypophysectomized animal is not normal with respect to its carbohydrate metabolism or muscle work performance, does not show the changes in lymphoid tissue seen in normal animals, nor does he resist environmental changes any better than the adrenalectomized animal. We may say then that the pituitary is necessary for normal secretion of the adrenal hormones. ACTH is the only agent by which control of the

adrenal cortex is effected; and it acts only in the presence of functioning adrenal tissue.

Recent evidence indicates a further elaboration on this relationship. It has now become possible with a variety of methods to obtain some idea of the relative rate of adrenal hormone secretion in various circumstances. We cannot yet measure the amount of hormone in the blood or its normal absolute rate of output, but we can make use of several indicators of adrenal gland activity. Some of these are a) the urinary excretion of derivatives of adrenal hormones, such as 17-ketosteroids or lipid soluble reducing substances, or so-called adrenal corticoids—substances active in promoting glycogen synthesis in the liver of adrenalectomized rats or mice; b) the level of circulating eosinophils or lymphocytes; c) in certain experimental conditions, nitrogen excretion or liver glycogen formation; or d) indications of ACTH activity in the adrenals of experimental animals. Of these the most used are the adrenal cholesterol and ascorbic acid concentrations. An example of this action is shown in Figure 3, where parallel effects of ACTH are seen on liver glycogen, blood lymphocytes, and the content of adrenal cholesterol and ascorbic acid.

The use of all of these methods clearly indicates one important fact —the rate of secretion of ACTH and hence of the adrenal hormones is not at all constant; but it is much increased by almost any stimulus or change in internal or external environment. Quite mild degrees of stress, so called, suffice to stimulate the pituitary. As Pincus and his collaborators found, merely getting out of bed in the morning is apparently the most severe stress of the day in normal sedentary men, as judged by lymphocyte and 17-ketosteroid responses. In some animals, quiet handling alone will have the same effect. Among other common types of initiating stimuli are exercise, pain, and emotional upsets, as well as allergic responses, infections, and the like.

The mechanism of firing the pituitary in response to these stimuli is at present the subject of much study and will not be discussed here. However, studies of this type and others have led to some revision of older views on the nature of adrenal physiology. Adrenal hormone secretion is not an all-or-nothing process, simply necessary for the well-being of the body, as was once thought, but the pituitary-adrenal relationship constitutes a most reactive system. Very large amounts of cortical hormone can apparently be put out on demand, to aid the

organism in making the adaptive responses required of it. Vogt has found in acute experiments in several species that the amount of hormone put out in adrenal vein plasma, as assayed biologically, is *per hour* several hundred times that amount which can be extracted from the gland after its extirpation. We do not know the degree of increase in the rate of secretion after any unusual provocation, but it must be very large. There is then here a considerable margin for error, so to speak, in our estimation of what *is* normal adrenal function. Future work should tell us whether, in treating diseased states with adrenal hormones, we are employing a pharmacological action of these substances or in fact are eliciting a true physiological response.

THE EFFECT OF ACTH* AND CORTISONE† ON CONNECTIVE TISSUE

CHARLES RAGAN, EDWARD L. HOWES, CHARLES M. PLOTZ**
KARL MEYER, J. WALLACE BLUNT and RAFFAELO LATTES

From the Departments of Medicine, Surgery and Surgical Pathology, Columbia University College of Physicians and Surgeons, and the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, New York, N. Y.

It has become apparent that the response of the mesenchymal or collagen diseases to the administration of ACTH or cortisone is not readily related to the known functions of the adrenal cortex involving electrolyte and carbohydrate metabolism. Adrenal function in these diseases is apparently within normal limits and a hyperadrenal state is the condition that effects the remission.

During the course of treatment of patients with lupus erythematosus disseminatus, periarteritis nodosa, dermatomyositis and rheumatoid arthritis, one of us noted delay in healing of incised wounds and depression of growth of granulations in open wounds.[1] The striae and poor wound healing occurring naturally in hyperadrenalism (Cushing's disease) also draw attention to the relationship between the hyperadrenal state and the integrity of the connective tissues.

In order to remove one of the variables—the disease state—and to observe the effect of induced hyperadrenalism on the connective tissues of normal animals, the following experiments were done. Normal rabbits were pretreated with cortisone for three days before skin defects were made in their ears, using the method described by Howes.[2] Similar skin defects were made in control rabbits which were treated in an identical manner except that they received no cortisone. The rabbits were killed at five and eight days after the wounds were made. In the control rabbit new granulations appeared to cover the blood vessels, whereas in the cortisone-treated rabbit no new granulations appeared,

Supported in part by grants from the Masonic Foundation for Medical Research and Human Welfare, the Medical Research and Development Board, Office of the Surgeon General, U. S. Army, and Office of Naval Research, U. S. Navy.

** Postdoctorate Research Fellow, National Institutes of Health, U. S. Public Health Service.

* Supplied through the courtesy of Dr. John R. Mote, Medical Director, Armour & Company, Chicago, Ill.

† Obtained from Merck & Company, Inc., through the Committee on Cortisone Research of the National Academy of Sciences. Purchased by funds from the U.S.P.H.S.

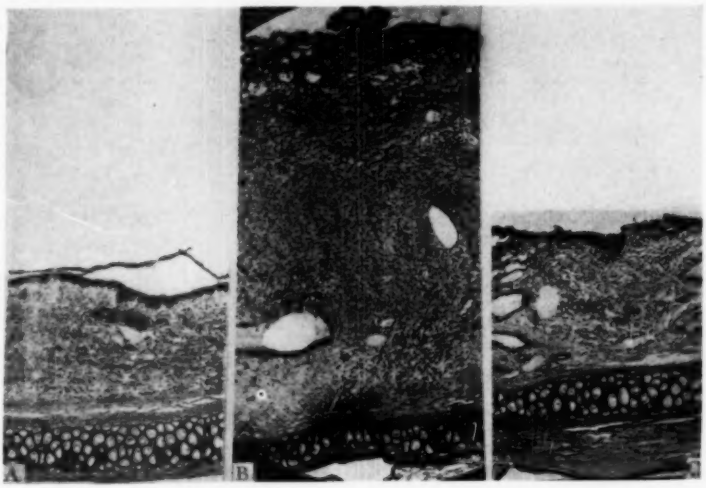


Fig. 1

A—Cross-section of normal rabbit's ear—left.
B—8-day granulating wound control—center.
C—8-day granulating wound, animal treated with cortisone—right.

Note thickness of connective tissue and the cell density in the normal ear. In the control wound the granulations are higher. There are many fibroblasts with collagen fibrils and many capillaries are seen. Two old large dilated blood vessels are present. The cortisone granulations are not much thicker than the normal connective tissue of the ear and all the old large blood vessels are dilated. Capillaries are present. However, cell concentration, particularly of the round type and those resembling fibroblasts, is increased. These cells show few signs of increased proliferation.

leaving the blood vessels exposed and visible except for a layer of fibrin. Histologically, in the control animals (Fig. 1b) there was a profuse growth of all elements of new connective tissue—fibroblasts, blood vessels, and ground substance, whereas in the cortisone-treated rabbit (Fig. 1c), all these elements were depressed. New fibroblasts were rare, new blood vessels were hardly seen and there was much less ground substance as determined roughly by the toluidine blue and Hale stains. Some new epithelium proliferated from the edges of the wounds. These rabbits were treated with large doses of cortisone, 25 mgm. daily, and manifested evidences of hyperadrenalism such as disappearance of circulating eosinophiles and moderate hyperglycemia, but ate well and were not ill. This dose of cortisone, obviously a very large dose, corre-

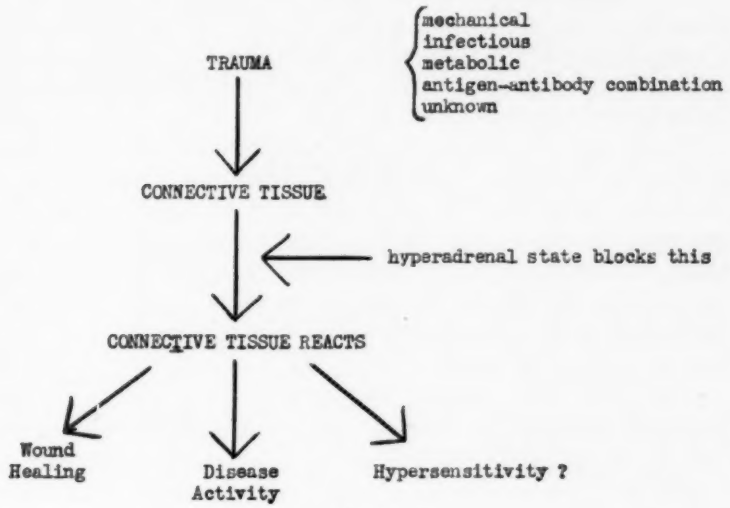


Fig. 2

sponds to 500 mgm. daily to a 50 Kg. human. However, similar results were obtained using 7.5 mgm. and 5 mgm. of cortisone daily, corresponding to the therapeutic human dose, although at the lower level granulations began to appear on the eighth day. In other words, with a lower dose there was delay in the appearance time of granulations rather than a complete suppression of growth.

A similar depression of regeneration of a mesenchymal tissue was demonstrated in rabbits using the experimental femur fracture technique of Hudack and Blunt.[3] With this technique, callus normally appeared four days following the fracture and was marked by the eighth day in control animals whereas in the cortisone-treated animals, the hemorrhage at the fracture site was not absorbed and there was little evidence of fibroplasia after eight days.

The mechanism whereby cortisone and ACTH lead to this suppression or decrease in reactivity of the connective tissue in response to trauma is not clear. The catabolic or anti-anabolic effect of hyperadrenalism on protein metabolism has been described and may reflect the decreased reactivity of mesenchymal tissues.

It is suggested that, in diseases involving mesenchymal tissue, these tissues are traumatized by some unknown agent. When hyperadrenalism is induced, the mesenchymal tissues are unable to respond to trauma, and a remission of symptoms resulting from the response of these particular tissues to such trauma follows.[4]

A diagramatic representation of this hypothesis is shown in Figure 2 whereby in the hyperadrenal state the connective tissue loses its ability to respond to trauma. This hypothesis serves to explain in part the response to the hyperadrenal state of disease entities with a wide spectrum of clinical symptoms and probably with widely different causative agents. In no way does this shed light on the etiologic traumatic episode which initiates rheumatoid arthritis. This remains unknown.

REFERENCES

1. Ragan, C., Grokoest, A. W. and Boots, R. H. Effect of adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis, *Am. J. Med.*, 1949, *7*:741.
2. Howes, E. L. Rate and nature of epithelization in wounds with loss of substance, *Surg., Gynec. & Obst.*, 1943, *76*:738.
3. Hudack, S. S. and Blunt, J. W. *Personal communication.*
4. Loeb, L. Hormones and the process of ageing, *Harvey Lect.*, 1940-41, *36*:228.

THE RELATIONSHIP OF ADRENAL CORTICAL ACTIVITY TO IMMUNE RESPONSES*

EDWARD E. FISCHEL

ONE year ago it would have been thought odd to consider the treatment of certain of the diseases discussed tonight with steroids of the adrenal gland. However, these diseases have long been thought to be related to immune processes[1-3] and the study of the effect of the adrenals on immunity has an enormous bibliography.[4, 5]

It is well known that patients with Addison's disease appear to be particularly vulnerable to relatively innocuous infections. By adrenalectomy, animals are rendered more susceptible to many noxious stimuli. Therefore, it is not surprising to find reports that such animals are more readily thrown into anaphylactic shock than are normal animals, either by antigen antibody reactions[6, 7] or histamine injections.[8] The lack of the adrenalin secreting mechanism that accompanied the loss of the adrenal certainly played a part in this altered susceptibility, but the cortex also appeared to be of significance, as suggested by substitution therapy experiments. In 1935, Wolfram and Zwemer[6] observed that the administration of adrenal cortical extract to adrenalectomized animals resulted in greater resistance to anaphylactic shock. This finding has been confirmed in many animal species, the most recent being the prevention of a type of anaphylactic death in mice by Dougherty.[9] Such studies emphasize the vulnerability of adrenalectomized animals to noxious stimuli and the value of replacement therapy, as Dr. Russell mentioned earlier this evening, but are too complex to permit an appraisal of specific effects on immune reactions. Whether the adrenal hormones influence the union of antigen with antibody, or influence the resulting reaction of the tissues might be studied more profitably in intact animals. They present fewer variables than do adrenalectomized animals and clinical studies suggest that the administration of cortisone

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, New York, N. Y.
Aided in part by grants from the Helen Hay Whitney Foundation and the Masonic Foundation for Medical Research and Human Welfare.

TABLE I—EFFECT OF ACTH ON THE ARTHUS REACTION PASSIVELY INDUCED WITH KNOWN AMOUNTS OF ANTI-OVALBUMIN NITROGEN (AbN) AND CRYSTALLINE EGG ALBUMIN.

Number of reactions of different severity related to total number of reactions in each group

Rabbits

	0.2 mg AbN		0.02 mg AbN			
	++++	+++	++	+	±	0
Control	9/10	1/10	1/10	6/10	1/10	2/10
ACTH:						
2 mg/day for 5 days	4/6	2/6		5/6		1/6
6 mg 6 hrs. before	6/6			5/6	1/6	
8 mg/kilo/day in 4 doses	4/4			2/4	2/4	

Guinea Pigs

	0.2 mg AbN		0.01 mg AbN			
	++++	+++	+++	++	+	0
Control	5/6	1/6		3/6	3/6	
ACTH:						
1 mg/day for 5 days	4/4			2/4	1/4	1/4
3 mg 6 hrs. before	4/4		1/4	2/4	1/4	
32 mg/kilo/day in 4 doses	2/3	1/3		3/3		

may have an effect on immune reactions even in the presence of intact adrenal glands. Employing Kabat's quantitative technique for the induction of anaphylaxis,[10] we have found no alteration from normal susceptibility to anaphylactic shock in intact guinea pigs treated with ACTH.* Using horse serum, which does not lend itself to the quantitative method, Leger, Leith and Rose[11] have reported a similar lack of effect of ACTH on anaphylaxis.

Anaphylaxis is not, perhaps, the best system to study as an example of an allergic reaction. Many investigators have looked upon rheumatic fever and to some extent rheumatoid arthritis as diseases that may perhaps be induced by antigen-antibody reactions of the *necrotizing* variety. A simple system by which the degree of tissue damage can be produced quantitatively in an expected way was established in studies with

* Adrenocorticotropic hormone was kindly furnished for these studies by Dr. Edwin E. Hays, Director, Biochemical Research, Armour & Company.

Kabat.[12] This reaction is the familiar Arthus reaction that results from the union of certain antigens with their antibodies in tissues. Rabbits and guinea pigs were sensitized passively with known amounts of rabbit anti-ovalbumin nitrogen locally; either 0.22 mg. of antibody nitrogen (AbN) to produce a severe reaction, or 0.02 mg. AbN for a minimal reaction. Subsequently a challenging injection of antigen (four times recrystallized hen ovalbumin) was administered intravenously. The site of the antibody injections became inflamed and were measured according to previous criteria.[12, 13] It is apparent from Table I that animals pretreated with ACTH in various doses did not have any appreciable difference from control animals in the severity of Arthus reactions, at either the severe or mild levels.

Another allergic system, nephrotoxic nephritis, has been studied in relation to cortisone administration by Knowlton and her coworkers.[14] No appreciable difference was noted in the nephritis when cortisone was administered either before or concurrently with the nephrotoxic antibody. Necrotizing allergic reactions in humans have been studied by several investigators. In our experience, skin sensitivity to tuberculin or to a streptococcal nucleoprotein fraction did not appear to be altered in patients receiving ACTH or cortisone in doses causing a remission of their underlying disease process. However, in one individual receiving very large amounts of ACTH there did occur an inhibition of the tuberculin reaction. This patient also developed widespread acne, hirsutism and the facies of Cushing's syndrome. The failure to elicit a tuberculin reaction here may be related more to the effect on connective tissue discussed by Dr. Ragan[15] than to an inhibition of an immune reaction.

At the present time, it appears that cortisone and ACTH do not alter the union of antigen with antibody. What effect, if any, might they have on antibody formation? There is much conflicting literature concerning the role of the adrenal cortical gland in the production of antibodies.[4] Perhaps most provocative was the report that under conditions of non-specific stress, or adrenal cortical activity, antibodies were increased in the circulation, apparently released from lymphocytes.[16] It appeared worthwhile to study this so-called anamnestic response with the more exacting disciplines of immunochemistry as introduced by Dr. Heidelberger,[17, 18] namely, the use of a single purified antigen and an analytical chemical technique for the determination of its antibody.

Accordingly with Drs. LeMay and Kabat,[19] a series of rabbits were

TABLE II*—THE EFFECT OF ADRENOCORTICOTROPHIC HORMONE ON THE ANTIBODY CONTENT OF SERUM, THE AMOUNT OF TOTAL WHITE CELLS AND OF LYMPHOCYTES. 25 MG. ADRENOCORTICOTROPHIC HORMONE GIVEN ON NOV. 13TH

	Rabbit	*August 1947*	*November 11*	*November 13*		*48 hrs. after stimulus*
				6 hrs. after stimulus	*12 hrs. after stimulus*	
C3	WBC		13,250	16,250	12,150	7,700
	Lymph		9,500	2,700	4,130	5,080
	μg. AbN/ml	170	2	0	0	0
S1	WBC		10,700	3,600		
	Lymph		6,250	685		
	μg. AbN/ml	180	10	3		
S3	WBC		10,350	15,000	5,190	
	Lymph		5,180	2,500	1,500	
	μg. AbN/ml	1,060	28	20	15	
SM	WBC		13,350	10,450	7,900	9,700
	Lymph		7,480	3,350	3,550	5,920
	μg. AbN/ml	320	18	11	12	11
X6	WBC		28,650	17,600	28,600	12,000
	Lymph		11,750	5,450	12,600	7,550
	μg. AbN/ml	210	12	10	10	10
N2	WBC		11,600	11,700	13,900	4,300
	Lymph		8,020	1,650	3,600	1,115
	μg. AbN/ml	63	0	0	0	0

* Reproduced from J. Immunol., 1949, 61, with permission of the authors,[19] the J. Immunol., and the Williams & Wilkins Co., publisher.

immunized with crystalline egg albumin and allowed to rest for three months. The antibody content of the serum at the end of the course of immunization is shown in the first column of Table II. After three months of rest, the amount of antibody nitrogen per ml of serum diminished appreciably to from zero to twenty-eight gamma. A single large dose of adrenocorticotrophic hormone was given. Although a fall in lymphocytes occurred, as indicated by the data in Table II, no increase in antibody was found. Indeed, if anything, a slight indication of a decrease was found in these animals as well as in a group given X-ray treatment instead of the ACTH. Drs. Eisen, Stoerk and their group,[20] also employing quantitative immunochemical methods, likewise reported that adrenal cortical extract failed to enhance circulating antibody.

Clinically, it is apparent that in several of the diseases associated with hyperglobulinemia a fall in the level of serum globulin is usually noted when cortisone or ACTH is administered. This appears to be in con-

tradistinction to the increase in globulin or in antibodies reported to occur in animals immunized concomitantly with the administration of cortical extract.[21]

With Drs. Bjørneboe and Stoerk, a small number of rabbits were immunized to pneumococcus by a technique which results in the rapid production of large amounts of globulin,[22] comparable in degree to that found in clinical hyperglobulinemia. In these animals, however, the increase in globulin is measurable as specific antibody globulin. One group of animals was given ACTH in a very small dose per day (between 0.5 and 1.0 mg.). Preliminary observations give evidence of an inhibition or diminution of antibody. Despite some overlap in individual titers, the mean antibody level of animals treated with ACTH was about half of that of the control group at the end of fourteen days and at the end of twenty-eight days. Dr. Stoerk[23] has independently studied the effect of cortisone on antibody production with results indicative of the same effect.

It is possible that this effect on antibody production may be one of the mechanisms by which cortisone alleviates rheumatoid arthritis and associated conditions, but this is highly speculative at the present time. The dramatic effects of cortisone on certain known allergic conditions such as hay fever and asthma, as recently reported[24] and as seen incidentally in certain of Dr. Ragan's patients, suggests that cortisone has a definite effect on immune mechanisms. Whether this effect occurs at the level of antibody production, at the level of the union of antigen and antibody or at any other point in the development of the immune response is not definitely established and should prove to be an interesting problem for further study.

Summary

The effect of adrenal cortical hormones has been studied in relation to several steps in the development of immune or allergic reactions.

1. Anaphylaxis, the Arthus reaction and other manifestations of the union of antigen with antibody were not appreciably altered.

2. An anamnestic response or non-specific increase in circulating antibody was not elicited by adrenocorticotrophic hormone.

3. An inhibition of antibody production may be produced by ACTH. Further study is necessary to substantiate this finding and appraise its significance in relation to the rheumatic and other diseases thought to be related to hypersensitivity.

REFERENCES

1. Zinsser, H., Enders, J. F. and Fothergill, L. D. *Immunity; principles and application in medicine and public health.* New York, Macmillan Co., 1939.
2. Klemperer, P. Pathologic-anatomic aspects of allergy, in Cooke, R. A. *Allergy in theory and practice,* in association with S. Baldwin et al.. Philadelphia, Saunders, 1947.
3. Fischel, E. E. The role of allergy in the pathogenesis of rheumatic fever, *Am. J. Med.*, 1949, *7:* 772.
4. Perla, D. and Marmorston, J. *Natural resistance and clinical medicine.* Boston, Little, Brown & Company, 1941.
5. Hartman, F. A. and Brownell, K. A. *The adrenal gland.* Philadelphia, Lea and Febiger, 1949.
6. Wolfram, J. and Zwemer, R. L. Cortin protection against anaphylactic shock in guinea pigs. *J. Exper. Med.*, 1935, *61:*9.
7. Dragstedt, C. A., Mills, M. A. and Mead, F. B. Adrenal cortex extract in canine anaphylactic shock, *J. Pharmacol. & Exper. Therap.*, 1937, *59:*359.
8. Marmorston-Gottesman, J. and Perla, D. Effect of injections of cortin on resistance of suprarenalectomized rats to large amounts of histamine, *Proc. Soc. Exper. Biol. & Med.*, 1931, *28:* 1022.
9. Dougherty, T. F. Presented at the A.A.A.S. meeting, December 29, 1949, New York.
10. Kabat, E. A. and Landow, H. A quantitative study of passive anaphylaxis in the guinea pig. *J. Immunol.*, 1942, *44:* 69.
    Benacerraf, B. and Kabat, E. A. A quantitative study of passive anaphylaxis in the guinea pig; the latent period in passive anaphylaxis in its relation to the dose of rabbit antiovalbumin, *J. Immunol.*, 1949, *62:* 517.
11. Leger, J., Leith, W. and Rose, B. Effect of adrenocorticotrophic hormone on anaphylaxis in the guinea pig. *Proc. Soc. Exper. Biol. & Med.*, 1948, *69:* 465.
12. Fischel, E. E. and Kabat, E. A. A quantitative study of the Arthus phenomenon induced passively in the rabbit, *J. Immunol.*, 1947, *55:* 337.
13. Benacerraf, B. and Fischel, E. E. Effect of phenergan (3277 RP) on the Arthus reaction in rabbits, *Proc. Soc. Exper. Biol. & Med.*, 1949, *74:* 349.
14. Knowlton, E.A.I., Loeb, E. N., Seegal, B. C. and Stoerk, H. C. *In preparation.*
15. Ragan, C. et al. The effect of cortisone on connective tissues. *Bull. New York Acad. Med.*, 1950, *26:*251.
16. Dougherty, T. F., Chase, J. H. and White, A. Pituitary-adrenal cortical control of antibody release from lymphocytes. An explanation of the anamnestic response. *Proc. Soc. Exper. Biol. & Med.*, 1945, *58:* 135.
17. Heidelberger, M. Quantitative absolute methods in the study of antigen antibody reactions, *Bact. Rev.*, 1939, *3:* 49.
18. Kabat, E. A. and Mayer, M. N. *Experimental immunochemistry.* Springfield, Charles C. Thomas, 1948.
19. Fischel, E. E., LeMay, M. and Kabat, E. A. The effect of adrenocorticotrophic hormone and X-ray on the amount of circulating antibody, *J. Immunol.*, 1949, *61:* 89.
20. Eisen, H. N., Mayer, M. M., Moore, D. H., Tarr, R. and Stoerk, H. C. Failure of adrenal cortical activity to influence circulating antibodies and gamma globulin, *Proc. Soc. Exper. Biol. & Med.*, 1947, *65:* 301.
21. Chase, J. H., White, A. and Dougherty, T. F. The enhancement of circulating antibody concentration by adrenal cortical hormones, *J. Immol.*, 1946, *52:* 101.
22. Bjørneboe, M. Serum proteins during immunization, *Acta path. et microbiol. Scandinav.* 1943, *20:* 221.
23. Stoerk, H. C. *Personal communication.*
24. Bordley, J. E., Carey, R. A., Harvey, A. M., Howard, J. E., Kattus, A. A., Newman, E. V. and Winkenwerder, W. L. Preliminary observations on the effect of adrenocorticotropic hormone (ACTH) in allergic diseases, *Bull. Johns Hopkins Hosp.*, 1949, *85:* 396.

CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

MARCH 1 and 2, 1950

ABSTRACTS

The Depressing Effect of Inositol on Serum Cholesterol and Lipid Phosphorus in Diabetics

WILLIAM C. FELCH and LOUIS B. DOTTI, Ph.D.

St. Luke's Hospital, N. Y.

Inositol, an essential vitamin and a lipotropic factor, has been reported to have a specific effect on cholesterol metabolism and to lower elevated levels of blood lipids. The relation of inositol to cholesterol metabolism is being studied at this hospital.

Thirty adequately controlled diabetic patients were selected at random from the diabetic clinic. Serum cholesterol, cholesterol esters and lipid phosphorus were determined on all subjects. When compared with a group of 100 normals, 18 (60%) of the diabetic group were found to have lipid levels above the range of normal.

The diabetics were then given inositol by mouth in doses of one gram three times a day for a period of eight weeks. All patients had a drop in the level of the measured serum lipids. The major portion of the drop usually occurred in the early weeks of administration. The higher the initial levels, the greater was the tendency to fall. At the end of eight weeks, all determinations were within the range of normal. The mean total cholesterol fell from 294 mgms. per cent to 244 mgms. per cent (normal=237 mgms per cent).

Preliminary results in a group of patients with arteriosclerotic heart disease would seem to indicate that inositol is also an effective lipid depressant in this condition.

The Effect of Venous and Arterial Occlusion on Digital Blood Flow

MILTON MENDLOWITZ and HAROLD ABEL

When blood flow is measured calorimetrically in the great toe or finger tip after release of sympathetic tone by indirect heating supplemented by intravenous tetra ethyl ammonium chloride, arterial occlusion maintained for two minutes or longer will decrease blood flow from 50 to 93 per cent. Venous obstruction on the other hand maintained for the same length of time decreases blood flow from 0 to 39 per cent. Similar differences, although less striking, are obtained with 10 to 30 seconds of arterial and venous obstruction. This indicates that venous obstruction as ordinarily performed may not trap all the inflowing arterial blood, a considerable proportion escaping probably via deep veins, and challenges the validity of venous obstruction plethysmography as a quantitative measure of blood flow.

Observations on the Mode of Thiocyanate Action: Augmentation by Mercurial Diuresis of the Hypotensive Effect of Thiocyanate

RICHARD GUBNER

Department of Medicine, Long Island College of Medicine, and
Medical Department, Equitable Life Assurance Society of the U. S.

The lowering of basal and casual blood pressure in hypertension by thiocyanate takes several weeks to become manifest, so that its action cannot be due to vasodilation. Attention has been drawn by Healy to the similarity of symptoms of clinical and experimental thiocyanate intoxication to the syndrome of adrenal insufficiency.

Adrenal function was investigated in the present study in hypertensive subjects who had been on thiocyanate therapy for several months (average blood level 8 mgms. per cent), employing the eosinophile count and response of eosinophiles to epinephrine (Laragh modification of Thorn test). Control eosinophile counts were normal, and an average fall in blood eosinophiles of 55 per cent occurred following epinephrine, which was identical with the responses in eight normal subjects. The eosinophile response is an index of 11-oxysteroid activity, but there is no evidence that the adrenal steroids are separately affected by pharmacological agents, so that this test serves as an index of over-all adrenal function.

The Robinson-Power-Kepler test of water and salt excretion provides an index of the activity of the salt retaining adrenal steroids in the absence of nephritis. This test was found to be decidedly abnormal in hypertensive subjects, with normal renal function, while receiving thiocyanate. This finding may be due either to a specific depression of the salt retaining hormones of the adrenal, or more probably, in view of the evidence of normal adrenal activity, to a decreased renal tubular re-absorption of salt with increased salt loss.

In addition to salt loss, urinary calcium and phosphate excretion were found to be increased by thiocyanate and blood calcium was significantly elevated, with a decrease in blood phosphorus. These findings, as well as the increased salt loss, are identical with those observed in parathyroid overactivity. Lassitude, muscular weakness and gastrointestinal symptoms, which are the principal side-reactions accompanying thiocyanate administration, are characteristic of hyperparathyroidism. Osteoporosis has been noted during thiocyanate therapy and attention is drawn to several other points of resemblance between the actions of thiocyanate and the parathyroid hormone. It appears likely that the locus of action of thiocyanate lies in renal tubular regulation of electrolyte excretion, similar to the effects of parathyroid hormone described by Albright, and Harrison and Harrison.

Intravenous dosage of 2 cc. of a mercurial diuretic augmented considerably the fall in blood pressure produced by thiocyanate, for periods up to several days. The hypotensive effect of thiocyanate therapy may be enhanced by the administration of small daily doses of an oral mercurial diuretic, best taken at bedtime since diuresis is increased by recumbency, and by liberal fluid intake since salt clearance in hypertensives is increased by a large urinary volume (Farnsworth). This regimen makes unnecessary the use of extreme dietary salt restriction, as in the rice diet, which is impractical in the clinical management of patients with essential hypertension.

Practical Clinical Application of a New Piezoelectric Material

GEORGE A. SHEEHAN, JR.
Red Bank, New Jersey

ABRAHAM I. DRANETZ, MSEE
Metuchen, New Jersey

FRANK K. PRIEBE, ME
Fair Haven, New Jersey

GLEN N. HOWATT
Metuchen, New Jersey

BALLISTOCARDIOGRAPHY

The doorway to the general use of the ballistocardiograph has recently been opened by the methods of Dock. This method of analysis of cardiac function and action has until recently been done by machines of too great a size and expense.

A modification of Dock's method is presented utilizing a piezoelectric system. This is a system which when it receives a mechanical strain becomes electrically charged and hence generates an electrical potential. Previously, the elements used were not stable, but with the introduction of barium titanate ceramic elements, there has become available a suitable material for this type of pickup.

The capacity of the element is .065 microfarads and can be increased if necessary. It can withstand temperature of 100 degrees without damage. The element is quite thin and does not affect the characteristics of the reed to which it is attached.

The instrument has the piezoelectric plates mounted on a metal strip which is attached cantilever fashion to a base. With the patient supine, the crossbar is placed across the patient's bare legs and against the bottom of the cantilever, bearing slight pressure against the latter.

The heart's recoil and the blood's impacts cause headward and footward displacement of the legs. When this occurs, the cantilever is bent one way or the other. A voltage is induced with each directional movement and is recorded by a standard electrocardiograph.

The electrical output of this system is of such a magnitude that should one wish to record velocity or acceleration, it is possible to introduce a relatively simple electrical network which would make this conversion.

Oral Treatment of Pernicious Anemia with Vitamin B_{12}

LEO M. MEYER, ARTHUR SAWITSKY, BERNARD S. COHEN, MENDEL KRIM, ROBERT FADEM and NORTON D. RITZ

From the Bronx Veterans Hospital, and the Third (N. Y. U.) Medical Division, Goldwater Memorial Hospital

Five patients with pernicious anemia in relapse were treated with daily oral doses of 75 to 150 micrograms of vitamin B_{12} for periods up to seven months. The reticulocytosis was submaximal but clinical and hematologic response was satisfactory. Improvement in neurologic status occurred in one of the cases showing evidence of combined system disease. One patient failed to respond to an oral daily dose of 150 micrograms and a second to quantities up to 250 micrograms a day. Both persons responded favorably to subsequent parenteral administration of vitamin B_{12}. Two other patients received 2 grams of desicated hog duodenum mucosa and 10 micrograms of vitamin B_{12} daily for 2 months. The reticulocyte response was suboptimal but the rise in hemoglobin and red blood cells was satisfactory. Clinical improvement occurred early in the course of treatment, and has continued. Two additional patients were given oral daily doses of 1.67 milligrams of folic acid and 25 micrograms of vitamin B_{12} for 5 weeks. The reticulocytosis was maximal and the rise in hemoglobin and erythrocytes rapid. Increase of leukocytes above 5,000 per cu. mm. was slow. Clinically the im-

provement was early and progressed favorably. Glossitis in one patient disappeared in a week and neurologic symptoms regressed soon after therapy was begun. A third patient has recently been started on treatment with the same combination of vitamins. He shows a similar clinical and hematologic response and an optimal reticulocytosis.

*A New Coumarin Anticoagulant (Tromexan) 4,4' dihydroxydicumarnyl ethyl acetate: Preliminary Report of Its Action**

GRAFTON E. BURKE and IRVING S. WRIGHT

From the Vascular Research Laboratory, Department of Medicine, Cornell University Medical College, New York

Since July 1949 observations have been made of the effect in animals and humans of a synthetic anticoagulant of the coumarin series, 4,4' dihydroxydicumarnyl ethyl acetate (Tromexan) which is a derivative of 3,3' methylenebis 4 hydroxycoumarin (Dicumarol). Tromexan is a colorless crystal, melting point of 173°C., and four to six times more soluble than Dicumarol.

Originally synthetized by Link, Overman et al. in 1942, Remis and Kubik, in 1945, Pulver and Von Kaulla in 1946, Payling Wright in 1949 have tested it clinically in Europe. The drug has been studied clinically for the first time in the United States in our laboratories. Pharmacological data reveal that the drug, per milligram, has about one sixth the potency of Dicumarol and is about one twentieth as toxic in animals. Ld 50 for single dose in mice is 750 mg/kg, in rats and rabbits 1.5-1.8 grams/kg. One hundred milligram doses in rats fed for 14-20 days failed to produce any toxic symptoms.

Three series of studies are herein reported: the administration of 1) varying single doses to rabbits, 2) single doses to normal humans, 3) therapeutic doses to patients with thromboembolic diseases. Observations were made on the anticoagulant and toxic manifestations of the drug. Complete pharmacological data will be reported elsewhere by Dr. Gruber of Jefferson Medical College.

The anticoagulant effect of the drug was measured by the Link-Shapiro modification of the Quick method. Determinations included the whole plasma and the 12.5 per cent plasma. Results were twice checked by separate technicians.

Animal Experiments: Because of individual and species variations rabbits were first standardized according to the technique of Link, Campbell and Overman. Resistant animals were eliminated. To the sensitive animals pH11 NaOH solutions of Tromexan was tube fed in doses of 100, 200, 300, 400, 500, 600 mgs. Prothrombin times were done at 6 hour intervals around the clock. No changes were noted in the first six hours. Slight elevations were noted in rabbits at the end of 12 hours while at 18 and 24 hours, consistent and reproducable prolongation of the prothrombin times were evident. The normal time (10-12 sec.) was doubled in 18-24 hours with readings of 22-24 seconds at 18 hours and 26-35 at 24 hours, depending upon dosage. Peak prolongations came at 30-40 hours with a return to normal in 12 to 18 hours thereafter.

Studies in Man: Normal control individuals were given single doses of 1200, 1500, 1800 mgs. Twenty four hours after administration of the larger doses the prothrombin times have uniformly reached a level of 25-35 seconds (undilute) and 65-100 (dilute). With doses of 1200 mgs. lower levels were achieved. The minimum time in which consistent changes in the undilute were effected was 15-18 hours. However some cases showed slight elevations (2-4 sec.) in the undilute and 6-12 seconds in the 12.5 per

* This work has been aided by grants from the S. H. Kress Foundation, the Lillia Babbitt Hyde Foundation, the Albert and Mary Lasker Foundation and the Hampl Foundation.

cent plasma 12 hours after the initial dose. No evidence of toxicity was evidenced in the normal group. Following a single dose the plasma shows a maximum in hypoprothrombin at 28-36 hours and returns to normal at 60-72 hours.

Fifty patients with thromboembolic disease including coronary occlusion, thrombophlebitis with and without embolic phenomenon have been treated. To date only one case, of severe Laennec's cirrhosis with coronary occlusion showed slight changes in his cephalin flocculation. No other cases showed immediate or delayed toxicity either clinically or as observed by red and white cell counts, sedimentation rates, urine analysis, PSP tests, BSP tests, cephalin flocculating thymol turbidity and total protein determinations.

An initial dose of 1200, 1500 and 1800 mgs. was usually given followed by a maintenance dose of 600-900 mgs. once a day. Some diurnal variation was evident on a single daily dosage, and a few patients required divided doses. With this regimen therapeutic hypoprothrombinemia (27-37) was usually achieved within 18-24 hours after initial dosage. It should be emphasized that no more than 24 hours should lapse between maintenance doses, except where the prothrombin time is excessively prolonged. Clinically the patients showed a satisfactory response to Tromexan as an anticoagulant.

This new coumarin derivative, Tromexan appears to be faster absorbed and excreted than Dicumarol. Further cooperative studies are now in progress.

The Diagnosis of Lymphogranuloma Venereum With Special Reference to the Complement Fixation Test

NORTON M. LUGER

Because of the inadequacy of clinical criteria alone in the diagnosis of lymphogranuloma venereum and because of the limitations of the Frei Test in differentiating active from old inactive infections, alternative laboratory methods have been sought.

The author studied a group of 31 patients diagnosed clinically as having inguinal lymphadenitis due to the virus of lymphogranuloma venereum, using the quantitative complement fixation test. In addition, three patients with extra-inguinal involvement were observed. All patients were treated with full doses of sulfadiazine for at least two weeks, and the serologic response to therapy was noted.

The procedure employed was a slight variant of that originally described by McKee, Rake, and Shaffer in 1940. Lygranum C. F., a commercially prepared antigen was utilized.

RESULTS

1. Of 31 cases of inguinal lymphadenitis, 80% had titres of 1:20 or more, on admission to the hospital. By the end of the second week, 94% of this group had titres of this magnitude.

2. Three cases of extra-inguinal disease, one of proctitis, one of a prolonged fever, and one of penile granuloma, all had titres of 1:40 or more.

3. In 22 cases, multiple serum samples were studied. Titre changes were noted in 13. In 5, fourfold or greater rises in titre occurred in the first two weeks. In 8, only titre falls occurred, and in 7 of these, the fall occurred after the second week.

4. In 7 cases, the C.F. test was positive before the Frei test.

CONCLUSIONS

The quantitative complement fixation test is a valid and specific test for lymphogranuloma venereum. It can be quantitated, and the data so obtained are of considerable help in diagnosing the disease. Titres of 1:20 or more are considered significant, as are fourfold changes in titre, whether they are rises or falls. Repeat determinations with observations for changes in titre will help differentiate recent from old infection. It is the best single laboratory test, clinically available at present, to confirm or eliminate the diagnosis of lymphogranuloma venereum.

The Lupus Erythematosus ("L.E.") Cell

S. L. Lee, S. R. Michael, I. L. Vural

The Mount Sinai Hospital, New York

The L.E. cell is the product of the interaction of the cellular elements of the peripheral blood or bone marrow and of a plasma factor, the latter unique for patients having acute disseminated lupus erythematosus.

The plasma factor has been demonstrated by us to be a gamma globulin, using the protein fractionation method of Svennson. This gamma globulin is frequently active in high dilution and can be titered. It is stable under temperatures varying from 0 degrees centigrade to 56 degrees centigrade. Complement is not required for its action. Spontaneous or induced remission may diminish its activity but in our series has not caused a complete disappearance of activity.

Serial studies indicate that the L.E. cell may begin as a peculiar autolytic process in one or all lobes of a polymorphonuclear leukocyte nucleus. In the former instances the whole development occurs within the given cell. The affected lobes undergo change, the altered cell becomes the center of a clump of apparently unaltered polymorphonuclear leukocytes, one or two of which ingest the material.

Previously published articles have emphasized the necessity of the presence of an anticoagulant for the formation of L.E. cells. We have been able to demonstrate L.E. cells taken directly from clotted blood of L.E. patients. The implications of this finding have not yet been explored.

Histochemical studies have been undertaken to define the nature of the ingested or altered material. By use of specific stains and absorption of appropriate monochromatic light, we have been able to show that the material is nuclear desoxyribosenucleic acid, partially intact and partially depolymerised, i.e., there is a differential absorption using Feulgen and methyl green stains. These findings relate the L.E. cell to the hematoxylin body.

Studies on Uterine Sinus and Amniotic Fluid Pressures in the Full-term Pregnant Uterus

Samuel S. Rosenfeld and Bernard Lapan

From the Departments of Obstetrics and Gynecology of the Lebanon and Jewish Memorial Hospitals

It seemed to us that a knowledge of the pressures in the uterine venous system would not only be of academic interest, but would most likely prove of practical value. With this in mind, we undertook a study of the pressures within the uterine sinuses, the intact amniotic sac, and pressure changes occasioned by intrauterine packing.

Materials and Methods

Patients were selected in whom elective cesarean section was to be performed. With the uterus exposed, a transfusion needle of the Unger or Kaliski type was inserted into a uterine sinus. In almost any area punctured, a venous flow was readily obtained. When blood was seen to flow freely, a standard spinal manometer was attached to the needle by means of a five inch length of rubber tubing, the manometer and tubing having been previously filled with 2.5 per cent sodium citrate solution. The reading was taken directly from the manometer. For the amniotic sac readings, the manometer was attached after amniotic fluid began to flow from the needle.

Pressure changes created by gauze packing were measured by means of a water filled balloon inserted into the uterine cavity and attached to the manometer system.

In ten cases, a comparison was made between the prothrombin time, sugar and urea in the uterine and general circulation, blood being drawn simultaneously from the uterine sinus and the antecubital vein. These determinations were discontinued after noting that there were no significant differences.

Uterine sinus pressures were determined in thirty-four patients. The lowest reading was 60 mm. of water and the highest 300 mm. of water, giving an average of 180 mm. of water.

The pressure in over 60 per cent of the cases was between 150 and 230 mm. of water.

The pressure of fluid in the amniotic sac was determined in six patients. In one case, the pressure was found to be 60 mm. of water and the other five ranged between 150 and 340 mm. of water.

In a patient in whom the uterine sinus pressure was found to be 60 mm. of water, the pressure rose to 120 mm. after the cavity was packed with five yards of gauze; to 170 mm. when the cavity contained ten yards; and to 295 mm. when the total gauze content of uterine cavity was fifteen yards.

We believe that the above findings may prove significant in the treatment of postpartum uterine hemorrhage. We are led to this belief by the physical fact that liquids cannot escape when a greater force is opposed to the open segment of a fluid system. An intrauterine pressure greater than the one in the vessel from which leakage is taking place should cause arrest of bleeding. Higher pressures can be readily obtained by means of gauze packing or an intrauterine balloon containing a sterile liquid.

*Treatment of Pulmonary Emphysema with Pneumoperitoneum**

M. G. Carter, E. A. Gaensler, and A. Kyllonen

Twenty-two patients with far advanced pulmonary emphysema and incapacitating dyspnea were treated with pneumoperitoneum. Three of these also had pulmonary tuberculosis and three were thoracic surgical patients whose postoperative course was complicated by severe emphysema and related inability to raise secretions.

Investigation before treatment consisted of extensive clinical evaluation of their cardio-pulmonary status and studies of pulmonary function, including determination of maximum breathing capacity, vital capacity and its subdivisions, and residual air.

Clinical observations after treatment revealed improvement in seventeen patients. This was characterized by lessened dyspnea, reduction of sputum, and increased exercise tolerance. All patients, including those not otherwise improved, noted increased tussive force and greater facility in raising tracheobronchial secretions.

The most characteristic physiologic changes after treatment were a marked reduction of the residual air, a notable increase of the complementary air and a small reduction of the total lung volume. The maximum breathing capacity was increased in all patients and the vital capacity was increased in some.

Pneumoperitoneum treatment was most effective in patients with diffuse "obstructive" emphysema. It was of least value in patients with marked pulmonary fibrosis and in those with single or multiple large blebs.

Other methods of treatment of pulmonary emphysema were reviewed, the technique of pneumoperitoneum administration was described, typical roentgen ray plates of the chest were illustrated and indications and contra-indications for this type of treatment were outlined.

* From the Thoracic Surgery Service, Boston City Hospital, Boston, the Physiology Sanatorium Division, Mattapan, and the Thoracic Service Hospital of St. Raphael, New Haven.

*Vagotomy Versus Gastric Resection: A Critical Evaluation of Two Methods of Surgical Treatment of Duodenal Ulcer**

MARTIN J. HEALY, JR., SIDNEY J. HELLMAN and PAUL K. SAUER

The present report attempts to evaluate critically the relative effectiveness of vagotomy alone and subtotal gastric resection alone as definitive elective surgical procedures for the patient with intractable duodenal ulcer. The material is derived from 263 consecutive subtotal gastrectomies performed at the U. S. Veterans Hospital, Bronx, New York, during the three-year period from January 1, 1945 to December 31, 1947. For comparion is a series of 54 consecutive vagotomies performed from August 30, 1946 through September 15, 1948, representing every vagus nerve section ever performed at this hospital. The following breakdown demonstrates the indication for operation in each of the sub-groups:

	Gastrectomy	*Vagotomy*
Duodenal Ulcer without obstruction	95	43
Duodenal Ulcer with obstruction	71	0
Gastric Ulcer	37	0
Marginal Ulcer	11	11
Emergency Bleeding Ulcer	2	0
Total All Ulcers	216	54
Malignancy	47	0
Total	263	54

In this analysis we are specifically concerned with the top listed group of 138 cases in which the indication for surgery was an intractable non-obstructing duodenal ulcer with or without bleeding. In this group 95 cases were treated by subtotal gastrectomy with three deaths, a case fatality rate of 3.2 per cent,—and forty-three cases by vagotomy with one death,—a case fatality rate of 2.3 per cent. Both groups are comparable not only as to the indication for surgery but also with regard to race, sex, age, general physical condition, and the surgeons performing the operations.

Excluding two cases of vagotomy which were combined with another operative procedure, follow-up was secured on 94.7 per cent of the cases treated by gastric resection and 100 per cent of the cases treated by vagotomy. Average follow-up period for the two groups was two and one half years.

In these two selected groups, the end results were as follows:

End Results		*Gastrectomy*		*Vagotomy*	
Excellent	—Symptom Free...	39	43%	8	19%
Good	—Mild Symptoms..	32	36%	14	34%
Fair	—Symptoms present but improved over preoperative status.....	8	9%	6	15%
	Total-Improved ..	79	88%	28	68%
Failure	—Complication requiring further surgery or recurrence of preoperative symptoms	8	9%	12	30%
Death	—Postoperative ...	3	3%	1	2%
	Total-Failure ..	11	12%	13	32%

It would appear from this analysis that despite its lower mortality rate, vagotomy is considerably inferior to gastric resection as a definitive procedure for the treatment of intractable duodenal ulcer.

* From the Surgical Service of U. S. Veterans Hospital, Bronx, N. Y. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Irradiation of Advanced and Radio-resistant Cancer through a Grid

HIRSCH MARKS

New York City Cancer Institute, New York

1. Irradiation through a grid has extended the range of x-ray therapeusis to tumors hitherto adjudged irresponsive to x-rays, namely:

a. Metastatic carcinoma of regional lymph nodes
b. Extra-vesicular extension of carcinoma of the urinary bladder
c. Recurrent inoperable pelvic carcinoma
d. Advanced intraoral carcinoma
e. Radio-resistant Hodgkin's disease.

To bring this to fruition, we substituted irradiation through multiple small fields for irradiation through large fields. The sizes of these fields are:—0.5 x 0.5 cm., 1 x 1 cm., and 2 x 2 cm. in a 10 x 15 cm. or 6 x 8 cm. lead-rubber shield, 3 mm. thick. The open portals alternate as in a checkerboard with as many covered areas. This effects a near-total elimination of back-scatter. The excessive absorption of the latter in the intervening normal tissue, is the real hindrance to the attainment of an adequate depth dose, as the full impact of the effective wave-length is brought to bear on the skin and subcutaneous tissues overlying the tumor. The narrowing of the irradiated volume results in an initial drop in intensity of the beam which is compensated by a 3, 6 or 12 fold increase in exposure.

2. Despite the enormous doses mentioned above, the hazards to the skin and normal tissues overlying the tumor of the patient are reduced to a minimum and the general systemic reactions are relatively non-existent. Desquamation and denudation of the skin follows after completion of 24,000r in air, and is the result of the back-scatter diffused from the depth of the tumor upwards. This is in contrast to irradiation through large fields where the same skin reactions result after a much smaller total dose, and the patient is subject to severe radiation sickness.

3. The over-all treatment time is greatly reduced by the delivery of higher daily doses, to wit, 600, 1200 and 2400r in air.

On the Deposition of Stilbamidine and 2-Hydroxystilbamidine in Cytoplasm and Nuclei of Different Organs and Tumors

I. SNAPPER, B. SCHNEID, E. GREENSPAN and F. LIEBEN, Ph.D.

Mt. Sinai Hospital

Administration of stilbamidine and 2-hydroxystilbamidine to patients with myeloma results in the formation of granules in the cytoplasm of the myeloma cells.[1, 2] These granules can be stained with Wright stain and have been proven to consist of ribose nucleic acid linked either with stilbamidine or 2-hydroxystilbamidine.[3] Quantitative methods for the determination of these diamidines in organs have been developed,[4] which made possible the study of the distribution of these substances in various organs of the body.

We were able to confirm the results of Hawking and Smiles,[5] who with qualitative methods found stilbamidine and 2-hydroxystilbamidine in liver and kidneys whereas in spleen and lungs only traces of the diamidines can be discovered. Because of the marked affinity of these diamidines to the liver parenchyma, the deposition of these compounds in a transplantable mouse hepatoma was investigated. It appears that after subcutaneous injection, considerable amounts of the diamidines can be found in the hepatoma. Therefore, the diamidines are de-

posited not only in the normal liver but also in a malignant tumor derived from liver cells. Other tumors behave differently. If mice bearing a transplantable lymphosarcoma, or a transplantable mammary cancer, are injected with these diamidines, the tumors contain only traces of these compounds.

Examination of imprints of organs of animals treated with these diamidines has elicited a remarkable difference between these two compounds. When these imprints are studied with a fluorescence microscope only small amounts of fluorescent material can be visualized in the animals treated with stilbamidine. Traces of fluorescing substance can be found in the cytoplasm only and sometimes between the cells. On the other hand, examination with the fluorescence microscope reveals large amounts of 2-hydroxystilbamidine in the organs of animals treated with this compound. This fluorescent material is partly present in the cytoplasm and between cells, but mainly in the nuclei. After injections with 2-hydroxystilbamidine the nuclei of liver cells, kidney cells and of the cells of the transplantable hepatoma become strongly fluorescent. After injection of 2-hydroxystilbamidine only small amounts of the fluorescent material are seen either in cells or in nuclei of lungs and spleen. The same negative result is obtained when imprints of the transplantable lymphosarcoma and mammary carcinoma are studied: after treatment with 2-hydroxystilbamidine no fluorescent material can be visualized in these tumors.

It can be surmised that the same distribution of the compound takes place in the organs of humans who are treated with 2-hydroxystilbamidine. We have observed that the nuclei of liver cells of such patients become highly fluorescent too. Nevertheless, we have seen that in humans, after treatment with 2-hydroxystilbamidine, the renal function as tested with phenolsulphonphthalein, and the liver function as tested with bromsulphalein test remained normal.

These diamidines are excreted in urine[6] and bile.[7] It could, therefore, be assumed that these substances are only accumulated in the cells of excretory organs. This might also be the reason for the accumulation of this substance in a hepatoma, a tumor derived from excretory cells. This assumption, however, is incorrect because large amounts of 2-hydroxystilbamidine can be visualized in the brain. In the brain of cancer mice treated with this substance large numbers of ganglion cells exhibit fluorescent nuclei. Unfortunately, the quantitative determination of 2-hydroxystilbamidine in brain substance, presents for the time being, great analytical difficulties. The accumulation of this diamidine in the brain may perhaps explain the trigeminal neuropathy which is a constant side action of another diamidine, that is, of stilbamidine.[8]

The difference between stilbamidine and 2-hydroxystilbamidine should be stressed. As far as can be seen stilbamidine links up only with the ribosenucleic acid of the cytoplasm and does not penetrate into the nuclei of the cells. The introduction of a hydroxy-group evidently increases the powers of penetration of the diamidine. Thus, 2-hydroxystilbamidine not only penetrates through the nuclear membrane and connects with the desoxyribose nucleic acid of the nuclei of liver and kidney cells, but it also reaches the brain which, as a rule, is well protected against the introduction of chemical substances.

REFERENCES

1. Snapper, I. and Schneid, B. *Blood*, 1946, *1*:534.
2. Snapper, I., Mirsky, A. E., Ris, H., Schneid, B. and Rosenthal, D. *Blood*, 1947, *2*:311.
3. Snapper, I. *J. Mt. Sinai Hosp.*, 1948, *15*:156.
4. Lieben, F. and Snapper, I. 1950 (*in press*).
5. Hawking, F. and Smiles, J. *Ann. Trop. Med.*, 1941, *35*:45.
6. Snapper, I., Tang, P., Saltzman, A. and Lieben, F. 1950 (*in press*).
7. Lawrence, J. *William Welch Lecture*, Mt. Sinai Hosp., 1949 (*not publ.*)
8. Sen Gupta, P. C. *Indian M. Gaz.*, 1943, *78*:537.
9. Arai, H. and Snapper, I. *New York State J. Med.*, 1947, *47*:1867.

Electrokymographic Studies of the Relationship Between the Electrical and Mechanical Events of the Cardiac Cycle

J. B. SCHWEDEL, P. SAMET, and H. MEDNICK

From the Cardiac Section of the Medical Service, Bronx Veterans Hospital

Studies of possible correlation between the electrical and mechanical events of the cardiac cycle have long been of interest. The initial modern studies were done by Wiggers[1] in 1923, and Lewis[2] in 1925 though earlier work had already been recorded.[3,5] Katz[6] made animal studies in which right and left ventricular pressures as well as pulmonary artery and aortic pressures were recorded by an optical manometer. Clinical studies correlating the electrocardiogram and carotid artery pulsations were done by Wolferth and Margolies.[7,8] These latter investigators assumed that left bundle branch block, as recorded on the electrocardiogram, would cause the left ventricle to contract later and therefore cause a later arrival of the pulse wave in the carotid artery than is normally the case. Nichol[9] made a similar study in 1933. Katz[10] criticized the work of Wolferth and Margolies. He employed the same technique but failed to note a correlation between the mechanical and electrical events of the cardiac cycle. Castex, Battro, and Gonzalez[11] attempted to correlate the site of origin of ventricular premature contractions with the interval from the onset of the QRS complex to the onset of the pulse wave in the carotid artery. Kossmann[12] in 1947 studied mechanical and electrical events of the cardiac cycle in the W.P.W. Syndrome.

The development of the electrokymogram allowed us to undertake such a study by a new technique. Ellinger and his co-workers[16] published a study of ventricular asynchronism as recorded by electrokymograms of the pulmonary artery and ascending aorta in 16 cases of bundle branch block, using the carotid artery pulsation as a reference point for comparison of the electrokymograms.

We have studied 25 cases of bundle branch block. By means of a new three-channel direct-writing recording apparatus and two electrokymograms, we have been able to record the electrokymogram of the pulmonary artery and ascending aorta simultaneously in the right anterior oblique position, thus eliminating use of the carotid artery pulsation as a reference point (as Ellinger and his co-workers[16] did) and thereby greatly increasing the accuracy of our measurements. In over 50 normals, electrokymograms of the two great vessels were made by this and other techniques and we found that the range of normal was from plus .03 to minus .02. That is, the upstroke of the pulmonary artery at the onset of its expansion was .03 seconds ahead of the upstroke of the ascending aorta at the onset of its expansion. In other cases the upstroke of the pulmonary artery was .02 seconds or .01 seconds ahead of the upstroke of the ascending aorta. In some the difference was .00, that is the upstrokes were equal in time. In others the upstroke of the ascending aorta was .01 seconds or .02 seconds ahead of the upstroke of the pulmonary artery, and these intervals we considered as negative, that is minus .02 and minus .01.

In the 25 cases of bundle branch block, we found that in only 8 cases was it possible to correlate the mechanical and electrical events of the cardiac cycles. In 17 of the cases, the relation between the onset of the pulmonary artery and the onset of the ascending aorta was within the normal range of limits. In all cases the diagnosis of bundle branch block was made from the standard and precordial leads, using the intrinsicoid deflection of the precordial leads to decide the side of the bundle branch block.

It is thus apparent that a correlation between electrical and mechanical events of the cardiac cycle is not possible, at least by this technique. It should be noted that in a case of right bundle branch block with a QRS of .12, that the pulmonary artery was .05 seconds ahead of the ascending aorta,

Results	Relation of Pulmonary Aorta and Ascending Aorta*	Correlation of Electrical and Mechanical Events
A. Cases of Incomplete RBBB. QRS Duration (QRS .11 or .12)		
1. .12	+.02	No
2. .11	+.04	No
3. .11	—.06	Yes
4. .11	+.03	No
5. .12	+.05	No
6. .12	—.02	No
B. Cases of Complete RBBB. QRS Duration (QRS greater than .12)		
1. .13	—.04	Yes
2. .14	—.09	Yes
3. .14	.00	No
4. .14	.00	No
5. .13	+.04	No
6. .13	.00	No
7. .15	.00	No
C. Cases of Incomplete LBBB. QRS Duration (QRS .11 or .12)		
1. .12	+.08	Yes
2. .12	+.03	No
3. .11	+.05	Yes
4. .12	+.02	No
D. Cases of Complete LBBB. QRS Duration (QRS greater than .12)		
1. .15	+.08	Yes
2. .14	+.01	No
3. .13	—.03	No
4. .15	+.02	No
5. .14	+.01	No
6. .13	+.06	Yes
7. .14	+.05	Yes
8. .14	+.02	No

* A plus sign means that the onset of pulmonary artery upstroke precedes that of the ascending aorta. A minus sign means the reverse.

well outside the normal range, but in a direction opposite to that expected if there were correlation between the electrical and mechanical events. In a case of complete left bundle branch block with a QRS of .13 seconds, the ascending aorta was .03 seconds ahead of the pulmonary artery, again a relation outside the range of normal but in a direct opposite to that expected.

Finally, it should be noted that repetition of the curves at different times leads to the same results—the results are reproducible.

REFERENCES

1. Wiggers, C. J. *Circulation in health and disease*, 2. ed. Philadelphia, Lea and Febiger, 1923.
2. Lewis, T. *The mechanism and graphic registration of the heart beat.* London, Shaw and Sons, 1925.
3. Stassen. *Arch. int. d. Physiol,* 1907, *5:* 60.
4. Fauconnier. *Arch. int. d. Physiol.* 1909, *7:* 462.
5. Eppinger and Rothberger. *Zentralbl. f. Physiol.,* 1910, *24:* 1055.
6. a Katz, L. N. *Am. J. Physiol.,* 1925, *72:*218.
   b. Katz, L. N. *Am. J. Physiol.,* 1925, *72:*655.
7. Wolferth, C. C., Margolies, A. and Bellet, S. *Tr. A. Am. Physicians,* 1933, *48:* 187.
8. Wolferth, C. C. and Margolies, A. *Am. Heart J.,* 1935, *10:*425.
9. Nichol, A. D. *Am. Heart J.,* 1933, *9:* 72.
10. Katz, L. N., Lanot, H and Bohning, A. *Am. Heart J.,* 1935, *10:*681.
11. Castex, M. R., Battro, A. and Gonzalez, R. *Arch. Int. Med.,* 1941, *67:*76.
12. Kossmann, C. E. and Goldberg, H. H. *Am. Heart J.,* 1947, *33:*306.
13. Henny, G. C. and Boone, B. R. *Am. J. Roentgenol.,* 1945, *54:* 217.
14. Henny, G. C., Boone, B. R. and Chamberlain, W. E. *Am. J. Roentgenol.,* 1947, *57:* 409.
15. Boone, B. R., Chamberlain, W. E., Gillick, F. G., Henny, G. C. and Oppenheimer, M. J. *Am. Heart J.,* 1947, *34:* 560.
16. Ellinger, G. F., Gillick, F. G., Boone, B. R. and Chamberlain, W. E. *Am. Heart J.,* 1948, *35:*971.

Ventricular Contraction in Wolff-Parkinson-White Syndrome: An Electrokymographic Study

SIMON DACK, DAVID H. PALEY and SIGMUND S. BRAHMS

From The Cardiovascular Research Group, The Mount Sinai Hospital, N. Y.

Ample evidence exists that in the Wolff-Parkinson-White syndrome there is premature activation of the ventricles (ventricular pre-excitation), usually of the right ventricle but occasionally of the left. There has been a great deal of disagreement, however, concerning the mechanical behavior of the ventricles, i.e., whether asynchronism of ventricular contraction results from pre-excitation.

The methods employed in the past for the detection of the presence or absence of ventricular asynchronism were based on the simultaneous recording of the venous and arterial pulse tracings, phonocardiogram, and electrocardiogram. By these tracings asynchronism was uniformly demonstrated in bundle branch block but uniform results were not obtained in Wolff-Parkinson-White syndrome. A more precise comparison of right and left ventricular ejection has recently been obtained by simultaneous recording of peripheral arterial pressure and right ventricular pressure during cardiac catheterization. No asynchronism was observed by this method in one case of Wolff-Parkinson-White syndrome.

The introduction of electrokymography has made available a simple and accurate method of determining ventricular asynchronism from the onset of the aortic and pulmonary kymographic curves which indicate left and right ventricular ejection, respectively. Normally there may be a physiological lag of ± 0.03 sec. between aortic and pulmonary artery ejection. This method has uniformly demonstrated the presence of mechanical asynchronism of the ventricles in bundle branch block, with a lag of 0.04 to 0.07 sec. between aortic and pulmonary artery ejection, depending on the bundle branch affected. It would be expected that if ventricular asynchronism were present in Wolff-Parkinson-White syndrome a similar lag between aortic and pulmonary ejection would be observed.

In an attempt to throw light on this disputed subject we have carried out detailed electrokymographic studies in 4 cases of Wolff-Parkinson-White syndrome with typical electrocardiographic features. By means of a 4-channel apparatus the electrokymogram was recorded simultaneously with the electrocardiogram, carotid pulse curve and phonocardiogram. The time of onset of the isometric and ejection phases of systole in the kymographic curves from the aorta, pulmonary artery, left ventricle and right ventricle in relation to the other reference tracings was measured.

In one case the aortic and pulmonary artery kymograms were simultaneous and in the other three cases pulmonary artery ejection preceded that of the aorta by 0.02 sec. The latter lag is within the normal physiological range. Analysis of the left and right ventricular kymograms yielded similar measurements. These observations indicate a lack of asynchronism in left and right ventricular ejection.

Our finding of absence of significant asynchronism of the ventricles in the presence of ventricular pre-excitation correlates well with the observations of the intracardiac and esophageal electrocardiograms in our cases recorded by Grishman, Steinberg and Kroop. These records indicate that there was pre-excitation not only of the right ventricle but also of the left in all four cases. This suggests that both ventricles are stimulated prematurely by aberrant impulses through accessory A-V pathways rather than through the His and Purkinje conduction system. The pre-excitation of both ventricles explains the lack of asynchronism in contraction in our cases.

Blood Volume and Electrolytes in Induced Acute Hypoglycemia in Diabetics

MILTON D. FELTENSTEIN, JOSEPH LITWINS, JULIUS POMERANZE, AARON SILVER and RALPH SCHWARTZ

Twenty-one patients, of whom 19 were diabetic and 2 non-diabetic, were rendered acutely hypoglycemic by intravenous injections of insulin. Before administration of insulin, control observations were made of blood volume and electrolytes and the urine was studied. After injection of insulin, frequent samples of urine and blood were examined until sugar fell to 40-50 mg. per cent and/or severe hypoglycemic symptoms appeared. Blood volume was determined by the dye method, initially with multiple doses of Congo-Red and later with Evans-Blue (T 1824). The findings were as follows:

A. Blood Electrolytes:
1. Ca invariably rose.
2. Inorganic P invariably fell.
3. Na rose in all but one case and in that patient there was no significant change.
4. K rose in all but one individual but there was no significant change in that patient.

B. Blood Volume:
1. Invariably reduced
2. The Hematocrit remained at the original level or was reduced.

C. Urine:
1. P excretion increased.
D. The non-diabetics showed the same serial changes as the diabetics.

In induced hypoglycemia in diabetics and non-diabetics, the inorganic P of the blood fell while the excretion of P in the urine rose. Despite the inadequacies of the dye method for blood volume determination, the consistency of our findings indicates a reduction in circulating blood volume. Unexpectedly, most of our cases showed a decreased and none an increased hematocrit, indicating that proportionately more red cells are removed from the circulating blood than plasma. The only parallel to such a fall in blood volume with decreased hematocrit, with which we are acquainted, is that in rabbits when shock is produced by suspending them by the hind legs.

CONCLUSIONS

Hypoglycemia produces a fall in blood volume of an unusual type in that the hematocrit falls as a result of a proportionately greater loss of red cells than plasma. The fall in hematocrit is unexplained. The reduction in circulating blood volume explains the rise of Ca, Na and K. The inorganic P of the blood falls while, pari passu, the excretion of P in the urine increases. Diabetics and non-diabetics react similarly to induced hypoglycemia.

From the Department of Medicine, Beth Israel Hospital, New York City.
Aided by a grant from the Albert B. Joffe Fund for Diabetics.

The Heritage in Otosclerotic Deafness

SAMUEL J. KOPETZKY

Director of Department and Professor of Otolaryngology
New York Polyclinic Medical School and Hospital

Biochemical blood pathologies are presented pertaining to clinical-pathological manifestations in 55 cases of deafened children, of whom 27 were deafmutes; the major number under 10 years of age.

Since 1860[1] geneological charts disclose the heritage of deafness, as an etiological factor in otosclerosis. What the heritage is,

and how it comes into being in succeeding generations have not heretofore been postulated.

Otosclerosis is generally *symptomatic*, presenting progressive deafness as its symptom. Autopsies show another form,—asymptomatic otosclerosis[2] which leaves its victims free of any consciousness of hearing loss.

Reporting 581 cases of deafness with 461 blood biochemical examinations,[3] *the factors at fault* which evolved otosclerotic lesions on the otic capsule and impaired sound perception, are *hyperpyruvemia* and *hypercholesterolemia*.

The children reported herein exhibited *hyperpyruvemia* without exception, thus disclosing a defective mechanism in carbohydrate metabolism *in the enzyme carboxylase*. This deficiency leaves cholinesterase out of control, and this destroys acetylcholine, the mediator of nervous action, along the synapses of the acoustic nerve. Cochlear and vestibular dysfunction results, exhibiting nerve-perception loss which is found on clinical examination.

The secondary phase in cellular pathology occurs because of the evidence furnished by hypercholesterolemia. The lack of lipotropic factors are the background; the deposits of lipids in the arterioles and capillaries of the end-organ apparatus happen because (1) there is deterioration in the health of the endothelial linings, and (2) anoxia of the parts, due to lipid deposits in the vascular supply to the cochlea. Atrophic areas form as a sequence to the deficiency outlined above; the intermediate carbohydrate metabolism of calcium is disarranged, and with phosphorus-calcium ratio imbalance, there occurs abnormal osteoblastic and osteoclastic activity with areas of bone rarefaction and new bone deposits abnormally placed in the layer of the otic capsule. Herein is found the explanatory data making comprehensible the meaning of the otoscopic and functional examinations. This relationship has not heretofore been realized.

From these blood studies, an estimate of the extent of cellular pathology can be made because in the writer's concept, enzymatic biochemical dysfunctions *precede the development of cellular pathology*, and once such dysfunctions are recognized, further evolution of the cellular pathology can at least be stopped by attempting a reversal of the chemical processes.

In many of the adult cases which constituted an earlier series of 581 cases, this has been achieved, with practical, useful gains in hearing acuity in a large number. In the present series of children, the progress is slower, because many of them never comprehended sound symbols, the meaning of which they must first be taught.

The acoustic nerve particularly, and to a lesser extent its vestibular branch, possesses an extremely low resistance power[4] as compared to other cranial nerves, as for example, the facial nerve. The acoustic nerve-end is the youngest in phylogenetic age. It easily succumbs therefore to deleterious environmental elements.

From the foregoing, it would seem desirable that young couples contemplating pregnancy who have a positive family history of deafness should undertake blood examinations and therapy to attempt reversal of biochemical blood pathology that may be uncovered to the end that the geneologic heritage may be removed before pregnancy is started.

REFERENCES

1. Duel, A. B., ed. *Otosclerosis, Resume of Literature to July 1928.* New York, Hoeber, 1929. Section II, Chapter 5.
2. Brühl, G. *Handbuch der Hals, Nasen- und Ohrenheilkunde.* (Denker, A. und Kohler, O.) Berlin, Springer, 1929, Part III, pp. 411, 432.
   Manasse, P. *Otosklerose.* Wien, Hölder, 1917.
3. Kopetzky, S. J. *Internat. Coll. Surgeons,* 1950, *13*:139.
   Kopetzky, S. J. *Deafness, Tinnitus and Vertigo.* New York. T. Nelson & Sons, 1948. Chapter VII, pp. 134 et seq. and 145; Chapter X, part 9, pp. 255 et seq. and 267 et seq.
4. Alexander, G. *Handbuch der Neurologie des Ohres* (Alexander, G. and Marburg, O.) Berlin, Urban, 1924, pp. 714-19.

Dihydroergocornine in the Differential Diagnosis of Functional Heart Disturbances and Organic Heart Disease

LEON PORDY, HAROLD S. ARAI, and ARTHUR M. MASTER

From the Cardiographic Department, The Mount Sinai Hospital, New York

The positive results after the "2-step" exercise electrocardiogram in patients with functional heart disturbance, that is, RS-T depressions and T wave inversions, may be indistinguishable from those observed in the presence of organic heart disease.

Ergotamine tartrate, previously used for making the distinction between organic and functional heart disturbance, was abandoned because of its anginal provoking properties. We have continued our study of this problem utilizing dihydroergocornine (DHO-180), a newer dihydrogenated ergot alkaloid derived from ergotoxine. The safety of this drug for clinical investigation in patients with organic heart disease was confirmed.

We first investigated the effect of intravenous administration of dihydroergocornine on blood pressure, heart rate and the resting electrocardiogram, including its influence on the "2-step" exercise electrocardiogram. Normal controls as well as cases of functional cardiac disturbance and organic heart disease were included in the series. Single injections of DHO-180 were given to 116 patients with repeated dosage on a subsequent day to seven of the subjects. The dosage of DHO-180 was 0.5 mgm. for 116 of the injections; for the remaining seven it varied between 0.25 and 1.0 mgm. The changes observed were found to occur within a few minutes following the intravenous injection, and lasted over one hour. In normotensive subjects the systolic blood pressure showed no significant alteration in half of the cases, and a slight to moderate drop in about two-fifths; the diastolic levels showed practically no significant change. On the other hand, in the hypertensives the systolic levels were decreased in three-fourths of the cases; changes in diastolic levels occurred in slightly less than half. The cardiac rate decreased in nearly all; in these instances the average maximum decrease in rate was -12.7 beats a minute. The resting electrocardiogram was entirely unaltered in one-half the cases; in almost all of the remaining half, there were noted only insignificant electrocardiographic changes (heightening of the T waves and, more rarely, slight RS-T elevations).

The precise explanation for the RS-T segment and T wave alterations in the functional cases remains unresolved as does the exact site of action of the dihydroergocornine. Both problems concern the intricate interrelationship between the autonomic nervous system and the cardio-vascular system, particularly the coronary circulation.

The side reactions to intravenous injection of dihydroergocornine were stuffy nose, nausea, and less frequently, dizziness and postural hypotension, all of which were transient.

The "2-step" exercise tolerance test was performed in a selected group of twenty patients both before and after the intravenous administration of 0.4-0.5 mgm. of dihydroergocornine. In ten of these who were classified clinically as having definite functional heart disturbance, the "2-step" test was positive before DHO-180 but negative after its administration. In the ten patients with unequivocal evidence of coronary artery disease the "2-step" test was positive before and after DHO-180 injection.

Because angina pectoris was not provoked in the organic patients and since there was constant prevention of electrocardiographic abnormalities after exercise by dihydroergocornine in the functional cases, this drug appears to be a safe and promising agent for further investigation in distinguishing functional from organic heart disease.

The Distribution of the Protein-bound Iodine in the Electrophoretic Fractions of Human Serum Studied with Radioactive Iodine

SOLOMON SILVER and MIRIAM REINER

From the Division of Chemistry, Laboratories of the Mount Sinai Hospital, New York City

Although it is generally accepted that the active hormone within the thyroid gland is contained in a specific globulin called thyroglobulin, no such unanimity prevails regarding the nature of the hormone as it actually circulates in the animal organism. The precipitin studies by Hektoen, Carlson and Schulhof and later by Lerman have not been a complete answer to this problem.

Earlier studies from this laboratory, using the relatively crude method of ammonium sulphate and sodium sulphate precipitation, showed that the proteins in the albumin and globulin fractions of the serum were both iodinated. Protein-bound iodine was determined by classical chemical methods.

We have now extended these studies using radio-active iodine. The blood serum of patients, several days after the therapeutic use of I-131, was dialyzed to free the serum of inorganic I-131. The sera were fractionated in an electrophoresis apparatus, the patterns photographed and the various fractions were then tested for their radioactivity which could only be due to the presence of I-131 incorporated in the thyroid hormone secreted after the administration of the radioactive iodine and circulating as protein-bound, presumably hormone, iodine. The specific activity of each protein fraction was then determined on the basis of the total radioactivity and the protein content of the respective samples.

Examination of Table I shows that the tagged circulating thyroid hormone is not uniformly dispersed through the plasma spectrum but that the various protein fractions are iodinated to varying degrees. The gamma globulin is practically free of organically-bound iodine while certain of the other globulin fractions are highly iodinated. We think that this is the first demonstration of the pattern of distribution of the protein-bound iodine in the serum of human subjects. We plan to supplement these studies with a determination of the stable iodine content of the various plasma fractions as isolated by Cohn. We wish to express our sincere thanks to Doctor Kurt G. Stern and Doctor Sergei Feitelberg for their very valuable cooperation in this study.

TABLE I—PROTOCOL OF STUDIES OF ONE SERUM

Electrophoretic Fraction	*Proteins Contained in Fraction*	*Per cent Protein*	*Corrected net counts per second per c.c. serum*	*Specific* Activity*	*Per cent total activity per mg. protein*
Left Upper	albumin alpha globulin	1.49	30.4	20.4	3.3
Left Middle	albumin, alpha, beta globulin	2.43	372.0	153.0	25.0
Left Lower	albumin, globulin	3.30	437.0	132.0	21.6
Right Lower	albumin, globulin	1.52	338.0	222.0	36.4
Right Middle	beta, gamma globulin	1.08	86.9	80.4	13.4
Right Upper	gamma globulin	0.19	0.5	2.6	0.4
Control Serum (dialyzed)	whole serum	4.12	506.0	123.0	

* Counts per second divided by per cent protein in sample
All counts in Q-gas counter

The Renal Clearance of Aureomycin in Man

JONAS H. SIROTA and ABRAHAM SALTZMAN

From the Medical Services and the Cardiovascular-Renal Research Group
Mount Sinai Hospital, N. Y.

Simultaneous renal clearances of aureomycin and endogenous "creatinine" were performed in ten subjects and of aureomycin, inulin and endogenous "creatinine" in five subjects convalescing from various infectious diseases requiring the oral administration of this antibiotic. Two hundred and fifty mgm. of the drug were ingested every four to six hours, the last dose being administered two hours before the onset of the clearance studies. The plasma levels of aureomycin ranged between 0.5 and 6.0 gamma/cc. with one extreme of 14 gamma/cc. in a subject with moderate renal insufficiency. In any one individual the plasma concentration varied little throughout the period of observation. In an additional five subjects aureomycin glycinate was administered as an intravenous drip and the renal clearances studied during rising and falling plasma concentrations of aureomycin through the range of 2.5 to 15 gamma/cc. Inulin was given as an intravenous infusion at rates calculated to maintain plasma concentrations of 30 mgm./100 cc. The renal clearances of inulin and endogenous "Creatinine" were used as measures of glomerular filtration rates.

Aureomycin concentrations in plasma and urine were determined by the fluoro-photometric method of Saltzman,[1] which has a maximum analytical error of 10 per cent and checks well with the biological method of Dornbush and Pelcak.[2] Inulin was determined by Schreiner's[3] modification of the resorcinol method and endogenous "creatinine" by the Bonsnes and Taussky[4] modification of the Jaffe reaction.

With the orally administered drug the aureomycin clearances averaged 44.5 per cent of the inulin clearances, with a range of 39.7 to 50.9 per cent, and 45.6 per cent of the endogenous "creatinine" clearances, with a range of 38.2 to 50.0 per cent. With the intravenously administered drug the aureomycin clearances averaged 38.8 per cent of the inulin clearances. In two of these latter subjects there was a moderate depression of the aureomycin/inulin clearance ratios at the higher aureomycin plasma concentrations. In the other three subjects the clearance ratios remained relatively constant throughout all ranges of plasma aureomycin concentrations studied. There appeared to be no correlation between urine flow and the clearance ratios in all of the fore-going studies. Preliminary studies suggest that the slightly higher clearance values obtained when the drug is administered orally, as compared to the intravenous route, may be due to the longer exposure to metabolic processes through the former route, with the production of degradation products of aureomycin which fluoresce but which may be biologically inactive and excreted in a different manner than the parent drug.

In 4 of the subjects receiving aureomycin by mouth mannitol osmotic diuresis was induced following three control periods. In all of these subjects no change was induced in the aureomycin/inulin clearance ratios, suggesting that tubular reabsorption of aureomycin does not play a significant role.

Ultrafiltrates were obtained from 6 plasma specimens drawn from two of the subjects receiving intravenous aureomycin. Analyses of these ultrafiltrates revealed that between 65 to 70 per cent of the drug was bound to unfilterable plasma components. The renal clearances of filterable aureomycin approximated the simultaneous inulin clearances closely, the average free aureomycin/inulin clearance ratios being 0.94 and 0.98.

It is concluded that the renal excretion of aureomycin occurs through glomerular filtration of the filterable fraction of the drug alone. It is cleared at approximately 45 per cent of the glomerular filtration rate when given orally, and at about 35 per cent of the glomerular filtration rate during intravenous administration. The rate of clearance of the drug is influenced solely by the glomerular filtration rate and the plasma

protein binding. Tubular mechanisms do not play a significant role. The excretion rate is not influenced by osmotic or water diuresis. For practical purposes therefore the urinary concentration of aureomycin in any one individual is directly proportional to the plasma concentration and inversely proportional to the urine flow.

REFERENCES

1. Saltzman, A. *J. Lab. & Clin. Med.*, 1950, *35*:123.
2. Dornbush, A. C. and Pelcak, E. J., *Ann. New York Acad. Sc.*, 1948, *51*:218.
3. Schreiner, G. *In preparation.*
4. Bonsnes, R. W. and Taussky, H. H. *J. Biol. Chem.*, 1945, *158*:581.

The Effect of Aureomycin Therapy in Infectious Mononucleosis (A Further Preliminary Study)

HAROLD A. LYONS, CDR, MC, USN.* and
EDWARD M. HARD, LT. (JG) MC, USNR

From the U. S. Naval Hospital, St. Albans, N. Y.

From preliminary studies and this further preliminary work, Aureomycin appears to be of definite benefit in the therapy of infectious mononucleosis. The protean nature of the manifestions of this disease make concrete evaluation of any new form of therapy difficult. Subjective and objective findings in control and aureomycin-treated groups are compared in this report.

We are reporting eighteen cases treated with Aureomycin and twenty-five control cases on symptomatic therapy and bedrest alone. Aureomycin was given in doses of 0.5 grams, four times daily for six days, in all but one patient who received only 0.25 grams, four times daily. For the large part of the series, control was established by alternating cases for control and special study series.

For lack of any one specific criterion to evaluate the progress of this disease, we have compared these manifestations:

a. Duration of hospitalization and duration of the course of the clinical disease.

b. Duration of fever.

c. Changes in total and differential leukocyte count.

d. Heterophile agglutination.

e. Splenomegaly.

f. Incidence and duration of hepatic involvement.

g. Effect of symptoms.

DURATION OF HOSPITALIZATION AND OF CLINICAL COURSE OF DISEASE.

The maximum, minimum and average for each of these groups is given in the following table:

Days of Hospitalization	*Maximum*	*Minimum*	*Average*
Without Aureomycin	161	10	39
With Aureomycin	67	10	26

Days of Disease	*Maximum*	*Minimum*	*Average*
Without Aureomycin	164	15	44
With Aureomycin	67	14	32

The significance of the difference in the average figures may be borne out by the fact that in the Aureomycin-treated group the disease was terminated in less than thirty days in 72 per cent of the cases as compared to 36 per cent in the patients receiving only symptomatic therapy. Duration of the hospital stay was comparable

* Chief of Research, U. S. Naval Hospital, St. Albans, L. I., N. Y. and Instructor in Clinical Medicine, Long Island College of Medicine.

in the two groups to the duration of the disease.

Duration of Fever: The duration of fever has shown striking alteration with use of Aureomycin therapy. With Aureomycin therapy 40 per cent of the patients returned to normal temperatures in twenty-four hours after treatment was started and 70 per cent within seventy-two hours. In the control group the shortest febrile reaction was four days and only 56 per cent were afebrile within fourteen days from the onset of the disease.

Total and Differential Leukocyte Count: There was no remarkable decrease in duration of abnormal leukocyte and differential counts in the Aureomycin treated group. In fact, in a few isolated cases the number of atypical mononuclear cells seemed to increase after the start of Aureomycin therapy. In both groups, the abnormal differential count and atypical lymphocytic cells lasted well into the convalescent stage of the disease.

Heterophile Agglutination: The heterophile agglutination titres were extremely variable in both groups. Of those cases receiving symptomatic therapy alone, 16 per cent developed no significant heterophile titre (1:128 or over).

This is consistent with other reports on the incidence of titre of heterophile agglutinins. Of those treated with Aureomycin, 44 per cent developed no significant titre, and in those who received Aureomycin within ten days of onset of the disease, 60 per cent did not develop a significant positive titre.

Splenomegaly: Splenomegaly was recorded in 24 per cent of the control group. This figure is difficult to record, because of the variable findings of the examiners. Of the Aureomycin treated group, enlargement of the spleen was absent in 66 per cent of the cases, and in those cases which received Aureomycin within the first ten days of the disease, 80 per cent remained free of splenomegaly. Two cases had an enlarged spleen before therapy with Aureomycin was instituted. No data is available concerning whether the spleen size decreased due to therapy.

Liver Involvement: Liver involvement occurred in 71 per cent of the control group, and in 75 per cent of the entire Aureomycin group, and in 67 per cent of the group receiving Aureomycin in the first ten days of the disease. However, the duration of hepatic involvement as determined by the usual laboratory tests for liver function is quite different for the two groups. In the control group, duration of abnormal liver function averaged seventy-six days with a maximum of 149 and a minimum of thirty-five days. In the Aureomycin treated group the average was twenty-nine days, and for those receiving Aureomycin in the first ten days of the disease, twenty-seven days.

Symptoms: Complete disappearance of symptoms within forty-eight hours or less occurred in the majority of cases and frequently within as little as six hours. In general the disappearance of malaise and other systemic symptoms paralleled the return of temperature to normal. Also, the post-infectious asthenia was considerably less in those patients who received Aureomycin.

Summary and Conclusions: From the data given above, although limited for so protean a disease as infectious mononucleosis, Aureomycin can be concluded to be effective in decreasing duration of fever, hospital stay, and total course of the disease by clinical measures. The subjective response in relief of symptoms within twenty-four to forty-eight hours also was very striking, although it cannot be evaluated in figures. It is felt that the duration of liver involvement is definitely reduced by Aureomycin therapy, as seen in a return to normal of the laboratory tests within approximately 36 per cent of the duration of the hepatic involvement in the control group.

The development of heterophile agglutination titre may be prevented to some extent by treating the disease early with Aureomycin. The abnormal blood picture and the atypical lymphocytosis apparently is not influenced by the drug.

This study is being developed further to include a larger number of cases, and also with attention to recurrence in control and Aureomycin treated cases.

The Diagnostic Value of Urinary Pepsinogen Excretion in Diseases of the Upper Gastrointestinal Tract

HENRY D. JANOWITZ, MILTON H. LEVY and FRANKLIN HOLLANDER, Ph.D.

From the Gastroenterology Research Laboratory, The Mount Sinai Hospital, New York, N. Y.

The excretion of urinary pepsinogen may have diagnostic significance in disorders of the upper gastrointestinal tract since patients with active duodenal ulceration excrete, on the average, four times as much urinary pepsinogen as do subjects without ulcer. Urinary pepsinogen (uropepsin), the proteolytic enzyme of urine which is active in the acid range of pH, originates from the gastric mucous membrane and is probably identical with gastric pepsinogen. The pro-enzyme contained in the peptic cells is partitioned into exocrine and endocrine fractions. The major portion, secreted into the gastric lumen, is converted to pepsin in the presence of HCl, in which form it cannot undergo gastrointestinal absorption. The smaller fraction of pepsinogen which diffuses into the tissue fluid enters the blood and is excreted in the urine as such.

We have measured the urinary pepsinogen excretion in 82 individuals, with and without upper gastrointestinal disorders, by means of Mirsky's modification of the Anson-Mirsky-Bucher method for estimating pepsin activity, using lyophilized bovine hemoglobin for the substrate as reported from this Laboratory. Measurements were made on urines collected for periods of 3 to 12 hours, either with the patient in the fasting state or 5 to 8 hours postprandially. A unit of uropepsin has been defined as the amount of enzyme which releases 1×10^{-4} mEq. of tyrosine from the hemoglobin substrate in 10 minutes at 37° C.; the present results have been expressed as units of uropepsin excreted per hour (U/hr.).

The 82 patients fell into six clinical categories, characterized as follows: (a) No gastrointestinal complaints nor demonstrable disease of the digestive tract (controls); (b) clinically active duodenal or marginal ulceration, confirmed by roentgen examination or at operation; (c) proven benign gastric ulcer; (d) malignant gastric neoplasms; (e) achylia gastrica of Addisonian pernicious anemia; and (f) total gastrectomy. The range of uropepsin excretion and the mean for each of these groups are as follows:

	No. of cases	*Range*	*Mean*	*($S.D._m$)*
(a) Controls	34	0-131	44	(± 6)
(b) Duodenal or marginal ulcer	31	115-373	187	(± 13)
(c) Gastric ulcer	4	43-125	87	
(d) Neoplasm	6	0-112	57	
(e) Pernicious anemia	6	0	0	
(f) Gastrectomy	1	0	0	

Ninety-four per cent (32) of the control group excreted less than 100 U/hr.; 97 per cent (30) of the subjects with duodenal or stomal ulceration put out more than 120 U/hr. In spite of the overlap of the ranges of these two groups, the difference between their means is statistically significant ($t = 9.59$, $n = 63$, $P < .0001$). The gastric ulcer and carcinoma groups, although they are small, both fall within the range for the control values. The last two groups represent patients incapable of elaborating gastric pepsinogen, and this is reflected by their failure to excrete uropepsin.

In view of the difference in excretion of pepsinogen in the duodenal and stomal ulcer group as compared with the non-ulcer group, this method appears to have diagnostic value, especially in subjects with gastrointestinal bleeding where other diagnostic procedures must be held in abeyance.

Bacteriologic and Epidemiologic Approach to the Treatment of Respiratory Infections With Aerosols of Specific Antibiotics

SAMUEL J. PRIGAL

New York Medical College, Flower-Fifth Avenue Hospital

In the treatment of sino-respiratory infection with penicillin aerosols, it was found that not all patients responded to this antibiotic. It was reasoned that failures were due in part to the presence of organisms not sensitive to penicillin. It was also noted that even after an excellent response to penicillin there were frequently early recurrences, particularly in children. In searching for the explanation of these repeated or continuous infections, despite treatment, the possibility of carrier states was considered, since it was frequently necessary to treat several members of the same family. A bacteriologic and epidemiologic investigation was, therefore, made of patients, and in selected instances of two or more members of a family.

For the purpose of expedience, cultures were limited to the pharynx; 163 patients were examined, and 225 cultures obtained in which 583 isolates were harvested. 563 of these isolates were exposed to the antibacterial action of penicillin, streptomycin and bacitracin. As aureomycin and chloromycetin became available, these were used in addition to the other antibiotics, so that 164 isolates obtained in 69 cultures were tested as well with all of the common potent antibiotics. The results are summarized in the following tables:—

TABLE I—CLASSIFICATION AND FREQUENCY OF 583 ISOLATES OBTAINED BY PHARYNGEAL CULTURES OF 163 PATIENTS

Organisms	*No. of Times Cultured*	*% of Frequency*
Streptococci:		
Alpha hemolytic	7	1.2
Beta hemolytic	39	6.6
Non-hemolytic	137	23.5
Straphylococci:		
Hemolytic (alpha & beta)	55	9.4
Non-hemolytic	104	17.8
N. Catarrhalis	110	18.8
Pneumococci	59	10.1
Proteus Vulgaris	29	4.9
Diphtheroids	16	2.7
Coliform Bacilli	9	1.5
Tetragenous	8	1.3
Friedländer Bacilus	6	1.0
Streptobacilli	2	0.3
Micrococci	2	0.3

TABLE II — INHIBITORY* ACTION OF PENICILLIN, BACITRACIN AND STREPTOMYCIN AGAINST 564 ISOLATES OBTAINED BY PHARYNGEAL CULTURE

Inhibitory Action	*No. of Organisms*	*%*
Penicillin only	7	1.2
Streptomycin only	37	6.5
Bacitracin only	10	1.7
Penicillin and not by Bacitracin	68	12.0
Bacitracin and not by Penicillin	64	11.3
Equally by Penicillin and Bacitracin	369	65.4
Bacitracin and not by Streptomycin	75	13.3
Penicillin and not by Streptomycin	73	13.1
Equally by Bacitracin and Streptomycin	361	64.0
Equally by Penicillin, Streptomycin and Bacitracin	305	54.0
Not inhibited by either Penicillin, Bacitracin or Streptomycin	20	3.5

* Concentration of antibiotic/cc in final broth dilution for inhibition studies were:

Penicillin— 1 unit
Bacitracin— 10 gamma
Streptomycin— 10 "

TABLE III — INHIBITORY* ACTION OF PENICILLIN, BACITRACIN, STREPTOMYCIN, AUREOMYCIN AND CHLOROMYCETIN (CHLORAMPHENICOL) AGAINST 164 ISOLATES OBTAINED BY PHARYNGEAL CULTURE

Inhibitory Action	*No. of Organisms*	*%*
Aureomycin	130	79.2
Chloromycetin (Chloramphenicol)	62	37.8
Penicillin	122	74.4
Streptomycin	121	73.7
Bacitracin	138	84.1
Aureomycin only	5	3.0
Chloromycetin only	0	0.
Penicillin only	1	0.6
Streptomycin only	6	3.6
Bacitracin only	2	1.2
Not inhibited by any antibiotics	3	1.8

* Concentration of antibiotic/cc in final broth dilution for inhibition studies were:

Penicillin—	1 unit
Bacitracin—	10 gamma
Streptomycin—	10 "
Aureomycin—	10 "
Chloromycetin—	10 "

SUMMARY AND CONCLUSIONS:

Pharyngeal cultures (225) obtained from 163 patients suffering from sino-respiratory infection netted 583 isolates; 564 of these were subjected to the inhibitory action of penicillin, bacitracin and streptomycin; 164 isolates were similarly treated and, in addition, tested with aureomycin and chloromycetin. Of the newer antibiotics, bacitracin and aureomycin proved to be highly efficient. Chloromycetin exerted relatively poor inhibitory action compared with these, or with penicillin or streptomycin.

No inhibitory action of any of these five antibiotics was noted against 3 organisms (1.8 per cent), nor against 20 organisms (3.5 per cent), when only penicillin, bacitracin or streptomycin were employed.

These facts indicate the value of culture and inhibitory tests as a guide to therapy.

In the contagious aspect of this study, forty-three people in seventeen family units were cultured 68 times, and 159 organisms isolated and identified. These studies reveal the possibility of the existence of a carrier state in ten of the seventeen families studied. This may account for repeated reinfection, or for chronic infection of the sino-respiratory tract as seen in practice.

TABLE IV—EVALUATION OF POSSIBLE EPIDEMIOLOGIC RELATIONSHIP OF 159 ISOLATES OBTAINED FROM 68 CULTURES IN 17 FAMILIES

No.	*Family*	*No. of Members of Family Cultured*	*No. of Patients with Pathologic Organisms*			*Possible Contagion*	*Pathologic Organism Involved*
			Complete	*Incomplete*			
1	*Sha.*	4	±		3	+	Hemol. Staph
2	*Mol.*	3		±	2	+	Hemol. Staph.
3	*Sch.*	2		±	0	—	None
4	*Mor.*	2		±	0	—	None
5	*Gol.*	3	±		2	+	Beta Hemol. Staph. & Diphtheroids
6	*Kam.*	2		±	2	+	Beta Hemol. Strep.
7	*Dem.*	2		±	0	—	None
8	*Blu.*	2	±		0	—	None
9	*Gow.*	3		±	0	—	None
10	*God.*	2	±		2	+	Pneumococci
11	*Sei.*	2		±	0	—	None
12	*Leo.*	2		±	2	+	Pneumococci
13	*Amb.*	3	±		2	+	Pneumococci
14	*Was.*	3		±	2	+	Hemol. Strep. & Pneumococci
15	*Tos.*	3		±	3	+	Pneumococci
16	*Coh.*	3	±		3	+	Pneumococci
17	*Sol.*	2		±	0	—	None
17		43	6	11	23	10	

The Effects of Experimental Acidosis on the Dynamics of the Circulation

KURT LANGE, FRANK GRAIG, VICTOR TCHERTKOFF and DAVID WEINER

From the Department of Medicine, New York Medical College and the New York Medical College Research Unit (Metropolitan Hospital)

Acidosis of the blood was produced in six dogs under artificial respiration by giving intravenous infusions of gluconic acid or acid sodium phosphate. The pH of the blood was thus lowered in steps and the behavior of the circulation investigated under these conditions. Acidosis within the range seen in diabetes and uremia produces a marked reduction in peripheral resistance which may decrease up to a fourth of its original value. Until very marked lowering of the pH is achieved, the mean blood pressure, taken with the Sanborn Electromanometer from the femoral artery, remains essentially constant. The minute output, determined according to Fick's principle by cardiac catheterization, increases up to three times its basic value. Since the pulse rate decreases slightly under acidification the stroke volume is increased still more markedly. As a consequence of the peripheral dilatation, the pulse pressure widens considerably. The venous pressure remains normal until extreme lowering of the pH to values of 6.8 or below is produced. When such severe acidosis is induced, the heart is unable to compensate for the further reduction in peripheral resistance, the blood pressure falls rapidly and the animal dies in a shock-like picture.

Generalized vasoconstriction produced in three dogs by induction of hypothermia can be relieved by lowering the pH of the blood.

The ability of the heart to increase its output to such an extent for considerable length of time without failing may be due to the increased oxygen dissociation accompanying acidosis.

These findings explain part of the circulatory phenomena, as seen in diabetic and uremic acidosis and coma, which so far were attributed mostly to dehydration.

The Adductor Longus Syndrome: A Cause of Groin Pain; Its Treatment by Local Block of Trigger Areas (Procaine Infiltration and Ethyl Chloride Spray)

JANET TRAVELL

Department of Pharmacology, Cornell University Medical College

In 50 patients with groin pain, the immediate source of this complaint was traced to trigger areas in the adductor longus muscle. Spasm and tenderness of this muscle were demonstrable. Pain referred from the upper third or half of the adductor longus was perceived deep in the groin, whereas the pain reference from its lower part extended also downward over the anteromedial aspect of the thigh and knee and at times over the pretibial region as far as the ankle. The pattern of pain reference was relatively constant from person to person, and was clearly demonstrated in these subjects by mechanical stimulation of the trigger areas at these sites, either by means of digital palpation or insertion of the needle within the muscle mass at the time of procaine infiltration.

Uniformly good results were obtained by local measures which block somatic trigger mechanisms. In most of the patients the trigger areas were infiltrated with a 0.5 per cent solution of procaine hydrochloride in

physiologic saline. In many instances, ethyl chloride spray was also used. The spray was lightly applied over the adductor longus muscle and groin in rhythmic upward sweeps in such a manner that frosting and cold pain were avoided. Gentle passive stretch was exerted on the muscle during spraying. In one patient, reported as "allergic" to procaine, groin pain was relieved by infiltration of the trigger areas with physiologic saline. In five patients, permanent relief of pain was secured by repeated (daily) application of the spray alone; in these subjects, the limitation of adduction of the thigh resulting from spasm of the adductor longus muscle, was seen to diminish or disappear at once, that is, during application of the spray. In other cases, when the spray produced no objective relaxation of this muscle, procaine infiltration was usually carried out immediately.

Relief of groin pain was permanent when spasm of the adductor longus muscle was caused by direct injury. When the spasm developed reflexly as the result of remote organic disease, relief of pain was usually temporary owing to constant reactivation of the vicious cycle of spasm-pain-spasm. Even in the latter group, which included 4 patients with metastatic carcinoma of the lumbar spine and pelvis and 4 patients with osteoarthritis of the hip joint, symptomatic relief was regarded by the patient as satisfactory. In osteoarthritis of the hip joint, instantaneous relief of nocturnal referred pain was obtained by the patient's applying the spray briefly whenever necessary during the night.

Thus, when muscular pain is relieved by such measures which block trigger mechanisms, no deductions can be drawn from that fact alone as to the primary cause of pain. It is only with the passage of time and further study of the patient that the differentiation can be made between a *physiologic* disorder of the myofascial tissues and a reflex cycle activated by remote *pathologic* lesions.

RECENT ACCESSIONS TO THE LIBRARY

("Possession does not imply approval.")

Aguilar Meza, Ricardo & Aguilar Meza, Ruben. Cancer y placenta. Guatemala, 1949, 118 p.

Amberson, W. R. & Smith, D. C. Outline of physiology. 2.ed. Balt., Williams, 1948 [1949], 502 p.

Aubry, M. Chirurgie de l'oreille, du nez, du pharynx et du larynx. 4.éd. Paris, Masson, 1949, 965 p.

Barrow, D. W. The clinical management of varicose veins. N. Y., Hoeber, [1949], 155 p.

Bergler, E. The basic neurosis: oral regression and psychic masochism. N. Y., Grune, 1949, 353 p.

Binger, C. A. L. More about psychiatry. [Chic.], Univ. of Chic. Press, [1949], 201 p.

Birkeland, J. Microbiology and man. 2.ed. Balt., Williams, 1949, 525 p.

Buxton, C. L. & Engle, E. T. Diagnosis and therapy of gynecological endocrine disorders. Springfield, Ill., Thomas, [1949], 62 p.

Canada. Department of National Health and Welfare. Industrial Health Division. A guide to the diagnosis of occupational diseases. [Ottawa, Cloutier], 1949, 317 p.

Clinical radiation therapy, edited by E. A. Pohle. 2.ed. Phil., Lea, 1950, 902 p.

De Kruif, P. H. Life among the doctors. N. Y., Harcourt, [1949], 470 p.

Dobbie, (Mrs.) B. M. (Willmott). Obstetrics and gynaecology. London, Hoeber, 1949, 358 p.

Goarnisson, J. Guide médical africain. Issy-Les Moulineaux, Presses Missionnaires, 1948, 572 p.

Hall, M. F. Public health statistics. 2.ed. N. Y., Hoeber, [1949], 441 p.

Hall, S. B. Psychological aspects of clinical medicine. London, Lewis, 1949, 416 p.

Hamilton, A. & Hardy, H. L. Industrial toxicology. 2.ed. N. Y., Hoeber, [1949], 574 p.

Hartshorn, W. M. The Class of 1902, College of Physicians and Surgeons, Columbia University. [New York], 1949, 1 v.

Huang Ti Nei ching su wên; the Yellow Emperor's classic of internal medicine. Chapters 1-34. Balt., Williams, 1949, 253 p.

Iason, A. H. Synopsis of hernia. N. Y., Grune, 1949, 500 p.

Jirásek, A. Náhlé príhody brisní. [Abdominal emergencies.] 3.vyd. V Praze, Melantrich, 1949, 522 p.

Johlin, J. M. Introduction to physical biochemistry. 2.ed. N. Y., Hoeber, [1949], 246 p.

Leighton, A. H. Human relations in a changing world. N. Y., Dutton, 1949, 354 p.

Macalpine, J. B. Cystoscopy and urography. 3.ed. Balt., Williams, 1949, 554 p.

Malnutrition and starvation in western Netherlands, September 1944-July 1945. The Hague, General State Print. Office, 1948, 2 v.

Modern trends in public health, edited by A. Massey. N. Y., Hoeber, [1949], 581 p.

Muller, M. L. Aan de poort van het leven; herinneringen van een vrouwenarts. Utrecht, Bruna, [1949], 243 p.

Paz Soldán, C. E. La O M S y la soberanía sanitaria de las Américas. Lima, [Universidad Mayor de San Marcos], 1949, 262 p.

Pharmaceutical Society of Great Britain. The pharmaceutical pocket book. 15.ed. London, Pharmaceutical Press, 1948, 427 p.

Puxon, (Mrs.) C. M. (Weddell). Handbook of midwifery. London, Sylviro, 1949, 326 p.

Readings in the clinical method in psychology, edited by R. I. Watson. N. Y., Harper, [1949], 740 p.

Seltzer, A. P. Your nasal sinuses and their disorders. N. Y., Froben Press, 1949, 155 p.

Stevenson, A. C. Recent advances in social medicine. London, Churchill, 1950, 241 p.

Stevenson, R. S. Recent advances in otolaryngology. 2.ed. London, Churchill, 1949, 395 p.

Stewart, C. P. & Dunlop, D. M. Clinical chemistry in practical medicine. 3.ed. Edinburgh, Livingstone, 1949, 324 p.

Taylor, A. S. Principles and practice of medical jurisprudence, edited by S. Smith. 10.ed. London, Churchill, 1948, v. 1.

Vallery-Radot, J. L. P.; Hamburger, J. & Lhermitte, F. Pathologie médicale. [Paris], Flammarion, [1948], 1408 p.

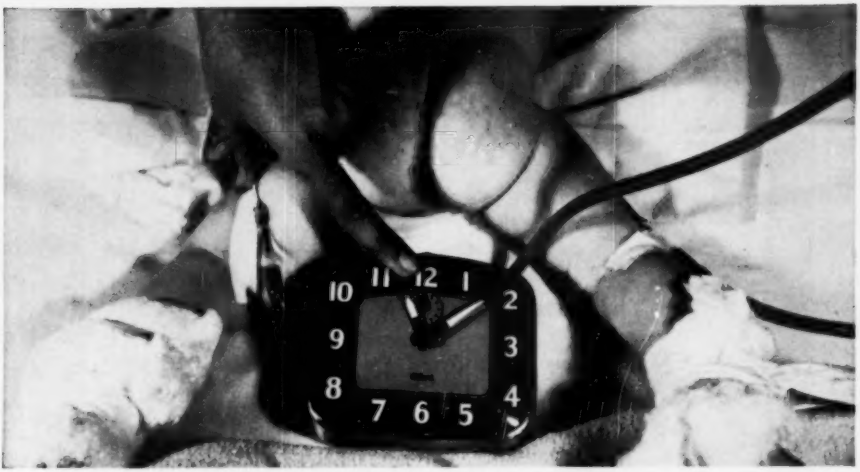
Voss, H. & Herrlinger, R. Taschenbuch der Anatomie. 2.Aufl. Jena, Fischer, 1948-1949, 3 v.

Williams, J. F. & Abernathy, R. Health education in schools. N. Y., Ronald, [1949], 316 p.

Wolf, G. D. The physician's business. 3.ed. Phil., Lippincott, [1949], 563 p.

Ziman, E. A. Jealousy in children; a guide for parents. N. Y., Wyn, 1949, 236 p.

Zoethout, W. D. Introduction to human physiology. St. Louis, Mosby, 1948, 424 p.



Demonstration[1] of effectiveness of Alidase in promoting absorption of fluid subcutaneously. Hypodermoclyses with saline were started bilaterally and simultaneously, the solution for the *left* thigh contained Alidase.

Ten minutes later the absorption of 250 cc. of fluid was complete in the left thigh, that in the right required 150 minutes. Note absence of swelling on the left, its presence on the right.

ALIDASE*—a highly purified, well-tolerated brand of hyaluronidase—permits hypodermoclysis at intravenous speed. Alidase increases the rate of fluid absorption "twelvefold."[2] Swelling, induration and discomfort are negligible when Alidase is employed.

1. Schwartzman, J.: Scientific exhibit at the American Academy of Pediatrics, San Francisco, Nov. 14-17, 1949.
2. Hechter, O.; Dopkeen, S. K., and Yudell, M. H.: The Clinical Use of Hyaluronidase in Hypodermoclysis, J. Pediat. 30:645 (June) 1947.

*Trademark of G. D. Searle & Co., Chicago 80, Illinois

SEARLE RESEARCH IN THE SERVICE OF MEDICINE

Growing in favor with physicians

Pabena* is *oatmeal* . . . and has the rich, full oatmeal flavor.

Like PABLUM,* PABENA is enriched with important vitamins and minerals and is thoroughly cooked and dried.

In addition, PABENA is valuable for infants and children who are sensitive to wheat. It is an ideal first solid food.

PABENA and PABLUM provide variety of cereal flavor that is welcomed by both mother and child.

PABENA and PABLUM, like all Mead's products, are not advertised in lay publications.

*T.M. Reg. U. S. Pat. Off.

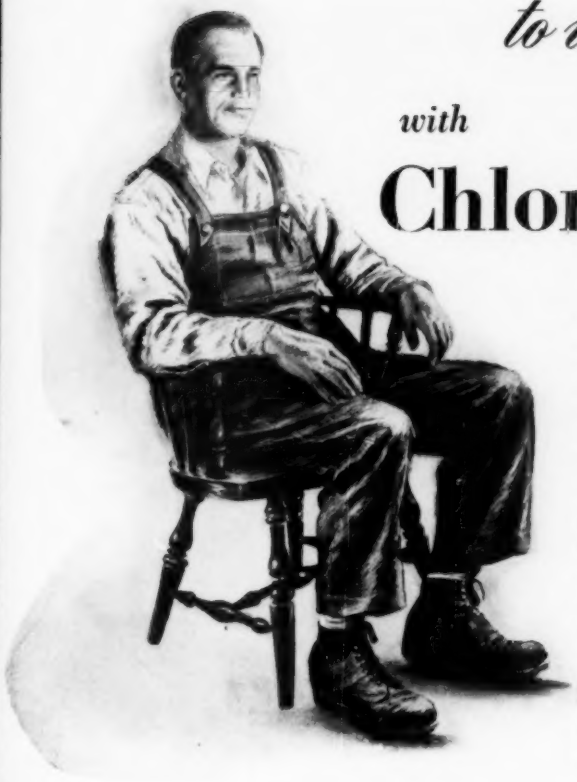
MEAD JOHNSON & CO.
EVANSVILLE 21, IND., U. S. A.

New York Office: MEAD JOHNSON & CO., Port of Authority Bldg., 111 Eighth Ave. Tel.: CHelsea 2-7272

He'll be back to work sooner...

with

Chloromycetin®



The cost of medication, of course, is but one item in the total cost of illness, the greatest expense stemming from the length of incapacitation and consequent loss of working time. One distinct advantage of CHLOROMYCETIN therapy is its fundamental economy—quick clinical response, reduced morbidity, shortened convalescence and earlier return of the patient to his job.

Particularly dramatic results are now obtained in a disease such as typhoid fever, where the illness formerly ran its course for several weeks because of the lack of specific therapy. The lengthy hospitalization, special nursing care, the supportive measures during this prolonged period—all have contributed to increased costs. However, CHLOROMYCETIN changes this: the duration of illness is greatly reduced, defervescence occurring within 2 to 3 days after treatment is begun. With control of the infection, general improvement is manifest and recovery is rapid.

The high degree of efficacy of CHLOROMYCETIN has also been demonstrated in a number of other diseases previously unresponsive or poorly responsive to treatment, such as acute undulant fever, urinary tract infection, bacillary and atypical pneumonia, typhus fever, Rocky Mountain spotted fever, scrub typhus, and granuloma inguinale.

PACKAGING

CHLOROMYCETIN (Chloramphenicol, Parke-Davis) is supplied in 0.25 Gm. Kapseals.® Descriptive literature on CHLOROMYCETIN is available to physicians on request.

PARKE, DAVIS & COMPANY

DETROIT 32, MICHIGAN

MEDICAMENTA VERA · P D & CO.

External Cod Liver Oil Therapy

DESITIN OINTMENT

Contains Crude Cod Liver Oil, Zinc Oxide, Talcum, Petrolatum and Lanolin

Used effectively in GENERAL PRACTICE for the treatment of Wounds, Burns, Indolent Ulcers, Decubitus, Intertrigo, Skin Lesions, Hemorrhoids, Anal Fissures, etc.

In PEDIATRICS for the treatment of Diaper Rash, Exanthema, Chafed and Irritated Skin caused by Urine, Excrements or Friction, Prickly Heat and in the nursery for General Infant Care.

Fatty acids and vitamins are in proper ratio, thereby producing optimum results. Non irritant, acts as an antiphlogistic, allays pain, stimulates granulation, favors epithelization. Under Desitin dressing, necrotic tissue is quickly cast off. Dressing does not adhere to the wound. In tubes 1 oz., 2 oz., 4 oz., and 1 lb. jars.

Desitin Medicinal Dusting Powder is super fatted with crude cod liver oil in a non irritating powder base. Indications: In infant care in the treatment of IRRITATED SKIN, SUPERFICIAL WOUNDS, DECUBITUS, INTERTRIGO, PRURITUS and URTICARIA. In 2 oz. Shaker-Top Cans.

Professional Samples on Request

For the Medical Profession

DESITIN CHEMICAL COMPANY

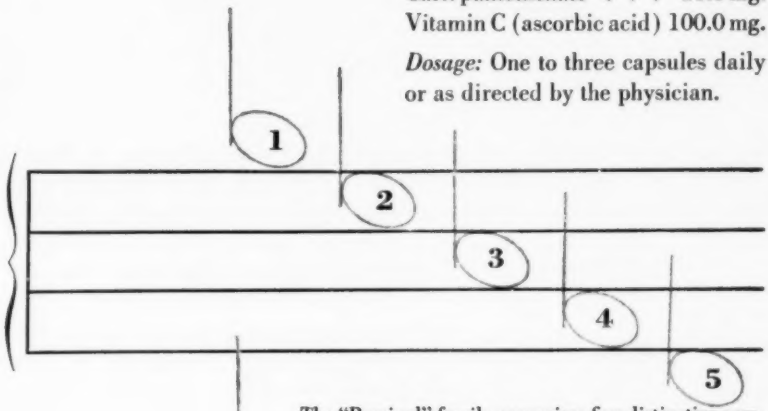
70 ELM STREET • PROVIDENCE • RHODE ISLAND

"Beminal" Forte with Vitamin C is recommended whenever oral administration of massive doses of B factors and vitamin C is desirable. Each capsule contains:

Thiamine HCl (B_1) . . .	25.0 mg.
Riboflavin (B_2)	12.5 mg.
Nicotinamide	100.0 mg.
Pyridoxine HCl (B_6) . .	1.0 mg.
Calc. pantothenate . . .	10.0 mg.
Vitamin C (ascorbic acid)	100.0 mg.

Dosage: One to three capsules daily or as directed by the physician.

forte!



The "Beminal" family comprises five distinctive combinations for the selective treatment of B deficiencies.

1. ***"Beminal"*** Forte with Vitamin C. Capsules No. 817
2. ***"Beminal"*** fortified with Iron and Liver, Capsules No. 816
3. ***"Beminal"*** fortified with Iron, Liver, and Folic Acid, Capsules No. 821
4. ***"Beminal"*** Forte Injectable (Dried) No. 495
5. ***"Beminal"*** Tablets No. 815

"Beminal" ® ***'B'*** ***for therapy***

Ayerst, McKenna & Harrison Limited

22 E. 40th St., New York 16, N. Y.

Don't Overlook the Obvious...

ORAL PENICILLIN THERAPY

Convenient · Acceptable · Effective

In the excitement over new antibiotics and new dosage forms of penicillin, the many advantages of oral penicillin therapy may often be overlooked. Yet this is one form of penicillin therapy that is highly acceptable to most patients. Penicillin tablets are easy to carry and easy to take—involve no painful injections nor expensive hospitalization. Recent clinical investigations have confirmed their value in many infections previously considered too serious for oral therapy.

Pfizer Tablets Buffered Potassium Penicillin G are available in foil-wrapped, hermetically sealed coverings in potencies of 50,000; 100,000; 250,000 and 500,000 units. For infants, children and aerosol therapy, Pfizer Soluble Tablets Potassium Penicillin G are available in potencies of 50,000 and 100,000 units. Troches Potassium Penicillin G properly flavored and buffered to assure pleasant taste, are supplied in aluminum-foil strips in potencies of 5,000, 10,000; 20,000 and 50,000 units.

Available through leading pharmaceutical companies. Chas. Pfizer & Co., Inc., 630 Flushing Avenue, Brooklyn 6, N. Y.

PFIZER

Manufacturing Chemists for Over 100 Years

Actuarially so!

You needn't be an actuary or statistician to be interested in comparative rates and figures. As a physician prescribing or injecting natural estrogens, you want the best at the most reasonable cost. Consider PROGYNON-B.®

PROGYNON-B is estradiol benzoate, derivative of the primary ovarian estrogenic hormone itself. No other injectable estrogen can compare with it in purity, potency and clinical efficacy.

PROGYNON-B

(Estradiol Benzoate U.S.P.)

What about cost? Did you know that PROGYNON-B is available, not only in ampuls, but also in the economical, multiple dose 10 cc. vial? There is a 10 cc. vial containing 20,000 R.U. (or 3.3 mg.) per cc. An injection of 1/2 cc. from this vial delivers 10,000 R.U. or 100,000 I.U.—at a cost *1/3 less* than the equivalent dosage from an ampul. With initial high dosage in this range, patients are relieved of menopausal symptoms with unusual rapidity, without untoward side effects, and at remarkably low cost.

PROGYNON-B is available in ampuls of 0.166, 0.333, 1.0 or 1.666 mg. (1000, 2000, 6000 or 10,000 R.U.), boxes of 3, 6, 50 and 100 ampuls; and in 10 cc. multiple dose vials containing 0.166, 0.333, 1.0 or 3.333 mg. (1000, 2000, 6000 or 20,000 R.U.) per cc., boxes of 1 and 6 vials.

Schering CORPORATION

BLOOMFIELD, NEW JERSEY

PROGYNON-B

SCHERING

More Red Blood from a Capsule....

HEMOSULES*

'WARNER'

Hematinic capsules for hypochromic anemias.

HEMOSULES* 'Warner' are high-potency, vitamin-rich capsules which also contain liver concentrate and highly absorbable ferrous sulfate.

Indications In Nutritional Deficiencies—*Hemosules** *'Warner'*
In Obstetrics—*Hemosules** *'Warner'*
In Gastroenterology—*Hemosules** *'Warner'*
In Infectious Diseases—*Hemosules** *'Warner'*
In Anemias of Acute or Chronic Blood Loss—*Hemosules** *'Warner'*
In all Secondary Anemias—*Hemosules** *'Warner'*

Dosage Two HEMOSULES* Capsules t.i.d. in well defined hypochromic anemias. One to three HEMOSULES* Capsules for prophylaxis and/or maintenance.

Formula Each capsule contains:

Ferrous sulfate, Dried U.S.P. 162.0 mg....(2.5 grs.)
Liver concentrate (1:20) 162.0 mg....(2.5 grs.)
*Folic acid**...0.75 mg.*
Thiamine hydrochloride (vitamin B_1)...1.0 mg.
Riboflavin (vitamin B_2)...1.0 mg.
Niacinamide...4.0 mg.
Pyridoxine hydrochloride (vitamin B_6)...0.5 mg.
*Calcium pantothenate**...0.5 mg.*
Ascorbic acid (vitamin C)...15.0 mg.

Package Information

Available in bottles of 96, 250 and 1,000

*Trade Mark
**The need for pyridoxine hydrochloride, calcium pantothenate and folic acid in human nutrition has not been established.
†The minimum daily requirement for niacinamide has not been established.

WILLIAM R. WARNER & CO., INC.

New York St. Louis

Herald Square, N. Y.

Parkchester, Bronx *Jamaica, Queens*

White Plains, N. Y. *Flatbush, Brooklyn*

MACY'S PRESCRIPTION DEPARTMENT

Macy's is up-to-the-minute. We make every effort to have all new or scarce drugs on hand for your prescription. We follow the development of each new product, obtain it as soon as it is available. And when you prescribe, you can be assured that your prescription is accurately compounded exactly as you write it, carefully checked by our supervising pharmacists.

No wonder so many physicians prefer Macy's Prescription Department.

Dilaudid hydrochloride

(dihydromorphinone hydrochloride)

COUNCIL ACCEPTED

Powerful opiate analgesic - dose, 1/32 grain to 1/20 grain.

Potent cough sedative - dose, 1/128 grain to 1/64 grain.

Readily soluble, quick acting.

Side effects, such as nausea and constipation, seem less likely to occur.

An opiate, has addictive properties.

Dependable for relief of pain and cough, not administered for hypnosis.

• Dilaudid is subject to Federal narcotic regulations. Dilaudid, Trade Mark Bilhuber.

Bilhuber-Knoll Corp. Orange, N. J.

HEAD COLDS SINUS

RELIEVES MANY NASAL CONDITIONS

BOROLEUM

Contains Menthol, Camphor, Eucalyptol, Methyl Salicylate, Boric Acid, and Petrolatum. All Ingredients U.S.P.

SINCLAIR PHARMACAL CO., Inc.
74 CORTLANDT STREET
New York 7, N. Y.

AND MINOR SKIN IRRITATIONS

SUN BURN DIAPER RASH

All Ingredients U.S.P.

An Ethical Product Having Many Uses and Recommended by the Medical Profession for over 35 years!

Samples will be sent upon request

Do you have YOUR copy of

THE NEW YORK ACADEMY OF MEDICINE

Its First Hundred Years

By DR. PHILIP VAN INGEN

EVERY Academy member should own this lively history of the first hundred years of this distinguished institution. Dr. Van Ingen has done a masterly job of tracing—from a huge mass of reports, records, annals, and minutes—the growth of the Academy from a small group of doctors to the influential organization of today.

"A personalized history by a scholarly writer with a thorough knowledge of his subject, critical independence, with, and an informal and adroit literary style."—W. B. McDaniel, II. *The New York Historical Society Quarterly.*

$10.00

Order direct from the publisher

COLUMBIA UNIVERSITY PRESS

2960 Broadway, New York 27, N. Y.

SHOE ALTERATIONS

FROM OUR PRESCRIPTION FILES...

When proper shoes, with or without alterations, are indicated you can recommend Pediformes with confidence.

R. Pediforme

REG. U. S. PAT. OFF.

FOOTWEAR

MANHATTAN 34 WEST 36th STREET
BROOKLYN 288 LIVINGSTON STREET
FLATBUSH 842 FLATBUSH AVENUE
EAST ORANGE — HACKENSACK — NEW ROCHELLE — HEMPSTEAD

Linguets should not be confused with ordinary tablets, which have been "proved relatively ineffective" by sublingual administration. ——

Escamilla, R. F. and Gordan, G. S.: Bull. Univ. California Med. Center, November 1949.

Linguets®

ECONOMICAL CONVENIENT HORMONE THERAPY

Androgenic

METANDREN® Linguets
methyltestosterone, 5 mg., white • 10 mg., yellow

Estrogenic

ETICYLOL® Linguets
ethinyl estradiol, 0.5 mg., pink

Progestational

LUTOCYLOL® Linguets
anhydrohydroxyprogesterone, 10 mg., yellow

Adrenal Cortex

PERCORTEN® Linguets
desoxycorticosterone acetate, 2 mg., green

LINGUETS® are specially shaped to fit comfortably into the buccal pocket; highly compressed to insure slow effective absorption of the hormone directly into the systemic circulation.

Ciba PHARMACEUTICAL PRODUCTS, INC.,
SUMMIT, NEW JERSEY

Patient under Treatment

FOR URINARY

TRACT INFECTION

meantime enjoys

Gratifying Relief

from distressing

symptoms

With orally administered Pyridium—an effective, *safe* urinary analgesic—physicians can give patients with urinary tract infection prompt relief from such symptoms as urinary frequency and pain and burning on urination.

Pyridium in therapeutic dosage is virtually nontoxic and may be administered throughout the course of treatment with streptomycin, penicillin, the sulfonamides, or other specific therapy.

Pyridium is the trade-mark of Nepera Chemical Co., Inc., successor to Pyridium Corporation, for its brand of phenylazo-diamino-pyridine HCl. Merck & Co., Inc. sole distributor in the United States.

The complete story of Pyridium and its clinical uses is available upon request.

Pyridium®

(Brand of Phenylazo-diamino-pyridine HCl)

MERCK & Co., Inc. Manufacturing Chemists RAHWAY, N. J.

In Canada: Merck & Co. Limited—Montreal, Que.

SARATOGA SPA

was built by the State to aid the private physician, in a primary or collateral capacity, in treating conditions for which hydrotherapy or crounotherapy is indicated. The Spa and its medical staff supervise the treatments prescribed by the individual physician — none of the staff engage in medical practice.

For literature write

WALTER S. MCCLELLAN, *M.D., Medical Director*
610 Saratoga Springs New York

THE STATE OF NEW YORK . . . THE SARATOGA SPA

for the successful treatment of . . .

LEG ULCERS

the DAXALAN-DOME-PASTE BANDAGE TECHNIQUE

AS INTRODUCED BY DR. WILLIAM M. COOPER, Director, Department of Peripheral Vascular Diseases—New York Polyclinic Medical School and Hospital.

This technique is based on a 3 point program—

1. Reduction of dermatitis with wet dressings of DOMEBORO TABS *(BUROW'S SOLUTION)*
2. Combat local infection and stimulate healing with thick application of DAXALAN in the center of the ulcer and surrounding areas.
3. Overcome venous insufficiency, stasis and edema by wrapping DOME-PASTE BANDAGE around the entire leg to supply compression.

DOME CHEMICALS INC. 230 EAST 43rd STREET NEW YORK 17, N. Y.
Makers of the Soothing, Modernized Form of Burow's Solution
DOMEBORO —Tablets • Powder • Packets • Ointment

tablets
ampuls
powder
suppositories

high theophylline content, ready solubility for rapid therapeutic effects in:

Bronchial Asthma
Paroxysmal Dyspnea
Cheyne-Stokes Respiration

dubin aminophyllin

(theophylline-ethylenediamine)

H. E. DUBIN LABORATORIES, Inc. 250 E. 43rd St., New York 17, N.Y.

Specialists in Plastic and Glass Artificial Human Eyes Exclusively

REFERRED CASES CAREFULLY ATTENDED

FRIED & KOHLER, Inc.

665 FIFTH AVENUE near 53rd Street
NEW YORK, N. Y. Tel. ELdorado 5-1970

Antiphlogistine

RUB A-535

A new counter-irritant and analgesic rub in a modern specially prepared base.

ANTIPHLOGISTINE RUB A-535 has been thoroughly tested both clinically and in more than 6,000 homes. It was created for the symptomatic relief of the aches and pains of Chest Colds, Arthritis, Rheumatism, Neuritis, Sprains, Sore Muscles, and Headaches.

RUB A-535 . . . contains four active ingredients: Camphor 1%, Menthol 1%, Oil Eucalyptus ½%, Methyl Salicylate 12%.

RUB A-535 . . . is a counter-irritant and analgesic which stimulates local circulation and brings comforting warmth by producing active hyperaemia in the areas to which it is applied.

RUB A-535 . . . has a new, modern non-greasy base which lets the product rub right in like a vanishing cream permitting instant utilization of the medications.

RUB A-535 . . . may be used for children as well as adults. It is pure white, stainless, and has a pleasant refreshing odor.

RUB A-535 . . . may be used following diathermy, infra-red lamps, baking, and other forms of physio-therapy. It is ideally suited for use between office treatments.

•

MAY WE SEND YOU, WITH OUR COMPLIMENTS, A FULL SIZE TUBE OF RUB A-535?

•

THE DENVER CHEMICAL MANUFACTURING COMPANY, INC.
Dept. K, 163 Varick Street, New York 13, N. Y.

As you know, "malted barley is rich in an enzyme which digests starch in the production of maltose."* Therefore, why not prescribe the beer that is brewed only from selected hops and fine barley-malt, *and no other grain?* Trommer's is one of the few all-Malt beers brewed in this country.

And along with millions of others, convalescents are sure to enjoy the lighter, cleaner taste of this fine *Premium* Beer.

*From "*Accepted Foods and Their Nutritional Significance*", by the Council on Foods of the American Medical Association.*

TROMMER'S

White Label *Premium* BEER

Brewed Solely of Malt and Hops

JOHN F. TROMMER INC., BREWERIES AT BROOKLYN, N. Y., ORANGE, N. J.

Doctors Are Showing

Increased Interest In*

WALKER-GORDON

CERTIFIED

LOW FAT *(Skimmed)* MILK

Walker-Gordon Skimmed Milk is simply Walker-Gordon Certified Whole Milk from which the cream has been removed. It contains all the nutrients in Certified Whole Milk except the butterfat and fat soluble vitamins. It contains all the minerals including calcium and phosphorus, all the water soluble vitamins, all the amino acids, practically all the proteins and about one-half the calories found in whole milk. It is unsurpassed as a source of high quality protein which is so important during pregnancy, lactation, period of rapid growth and old age.

* AN ACTUAL SURVEY of 8,500 physicians in the New York City area has shown that Walker-Gordon Certified Skimmed Milk is widely used by the Medical Profession. The following uses were mentioned in the survey: Pregnancy and Lactation, Obesity in Children and Adults, Abnormal Bile Secretion, Celiac Disease, Infant Feeding Cases, Gastric Ulcers, Diarrhea, Psoriasis, Allergy, Diabetic Diets, Colitis, Acne, Eczema, and Hypertension.

Walker-Gordon Certified Skimmed Milk is handled by many leading dairy distributors in New York, New Jersey and Pennsylvania. Write or phone

WALKER-GORDON LABORATORY COMPANY

Plainsboro, N. J. **Tel. Plainsboro 2750**

THE INDICATION DICTATES THE CHOICE OF MEDICATION

Glycerol (Doho) by exclusive process has the highest obtainable specific gravity and is virtually free of water, alcohol and acids

IN ACUTE OTITIS MEDIA
REMOVAL OF IMPACTED CERUMEN
AS AN ADJUNCT TO SYSTEMIC ANTI-INFECTIVE THERAPY, AS PENICILLIN, ETC.
CONTAGIOUS DISEASE EAR INVOLVEMENTS

USE *Auralgan*

... because its potent decongestant, dehydrating and analgesic action provides quick, efficient relief of pain and inflammation in any intact drum involvement.

FORMULA:

Glycerol (DOHO) (Highest obtainable spec. grav.)	17.90 GRAMS
Antipyrine	0.81 GRAMS
Benzocaine	0.21 GRAMS

IN CHRONIC SUPPURATIVE OTITIS MEDIA, FURUNCULOSIS AND AURAL DERMATOMYCOSIS

USE **O-TOS-MO-SAN**

... a potent chemical combination (*not a mere mixture*), combining Sulfathiazole and Urea in AURALGAN Glycerol (DOHO) Base—because it exerts a powerful solvent action on protein matter, liquefies and dissolves exuberant granulation tissue, cleanses and deodorizes, and tends to exhilarate normal tissue healing in the effective control of chronic suppurative otitis media.

FORMULA:

Urea	2.0 GRAMS
Sulfathiazole	1.6 GRAMS
Glycerol (DOHO) Base	16.4 GRAMS

Literature and samples sent to physicians on request.

DOHO CHEMICAL CORP. Makers of AURALGAN and O-TOS-MO-SAN NEW YORK 13

CHARLES B. TOWNS HOSPITAL *Established 1901*

FOR THE TREATMENT OF ALCOHOLISM

NARCOTIC AND BARBITURATE

ADDICTIONS EXCLUSIVELY

Complete Medical & Psychiatric Treatment at predetermined cost. Privacy of patient is assured—if desired.

Literature on Request

Wm. D. Silkworth, *Medical Director*
Edward B. Towns, *Director*

293 Central Park West, N. Y. 24, N. Y.
SChuyler 4-0770

Member American Hospital Association

MAGER & GOUGELMAN, INC.

FOUNDED 1851

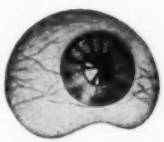
510 MADISON AVENUE • NEW YORK 22, N. Y. • PLaza 5-3756

Specialists in the manufacturing and fitting of

PLASTIC AND GLASS EYES

The New Magnetic Implant Designed by Dr. Troutman

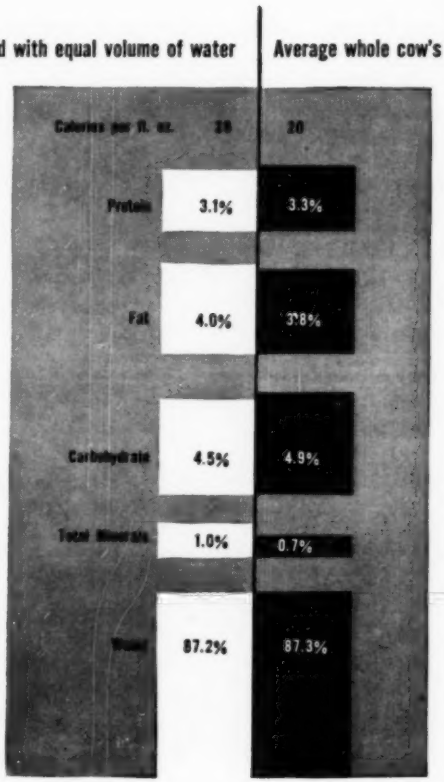
Reprints and Catalogue Available



PARTICULAR ATTENTION GIVEN TO FITTING
PROSTHESIS FOR MOTILITY IMPLANTS

Not just milk replacement but casein replacement...

Casein—and also lactalbumin—are frequently the cause of hypersensitiveness to cow's milk. This hypersensitiveness can be manifested by gastrointestinal upsets followed in time by eczema of a mild or acute nature. In such cases cow's milk of all types must be eliminated from the diet. Mull-Soy is a near equivalent for milk to be used in these cases.



A scientifically sound formula for avoidance of casein allergy

Stable—vacuum packed

High in unsaturated fatty acids essential for growth

Pleasant-tasting

A homogenized liquid, not a powder or a hydrolysate

For hypoallergenic diet in infants or adults look to

MULL-SOY®

The Borden Company
Prescription Products Division
350 Madison Avenue, New York 17

At drugstores in 15½ oz. tins.

because it combines all 3
Pectin—enhances hydrophilic properties
Colloidally dispersed in a special adsorbent alumina gel
Purified Kaolin

KAOMAGMA with PECTIN

is effective in Control of Diarrhea

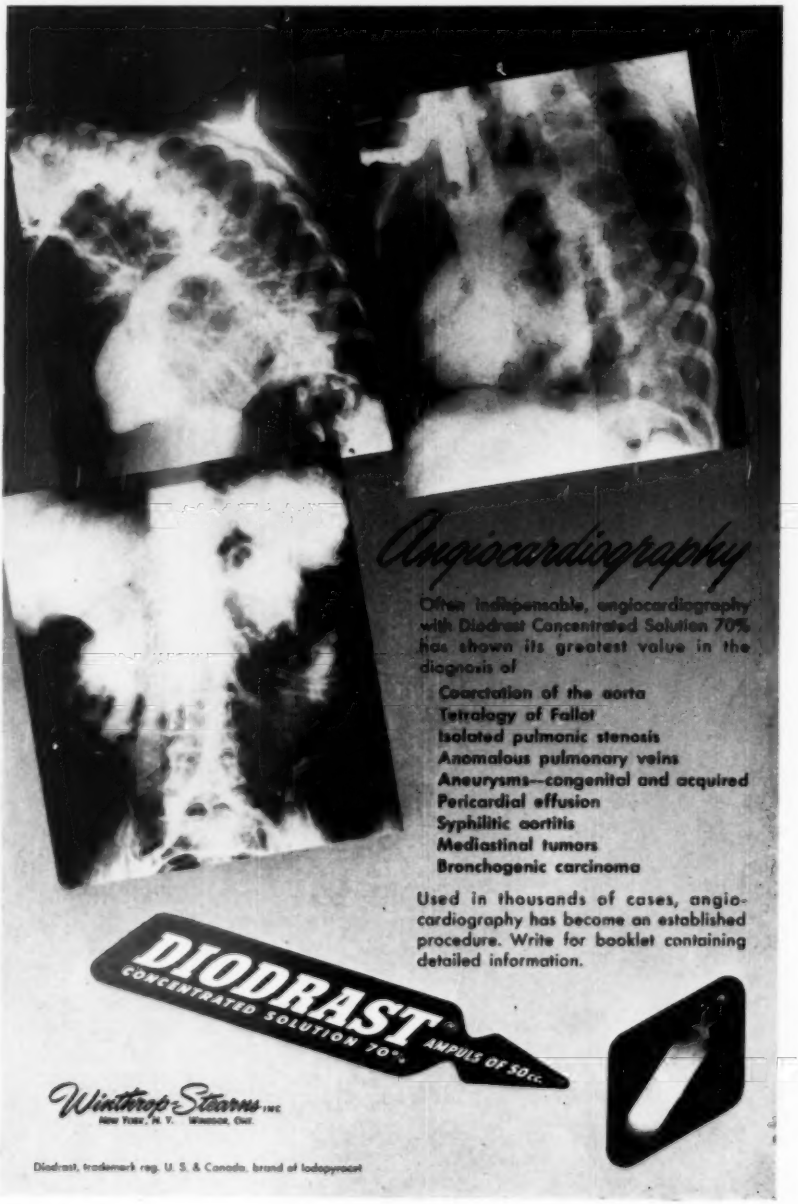
Relief is quick . . . Kaomagma with Pectin soothes and protects inflamed intestinal mucosa. Cramps and distention are promptly relieved.

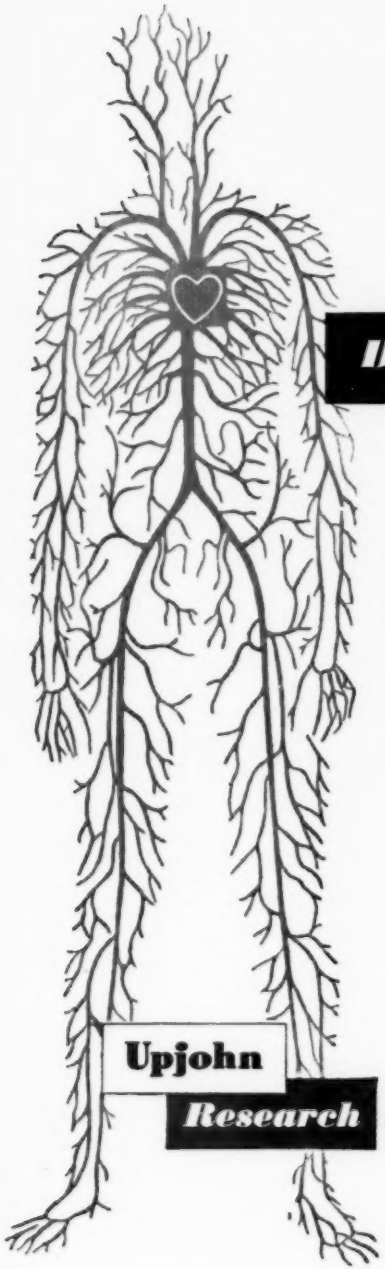
Consolidates stools . . . checks fluid loss . . . restores patient's comfort.

Bottles of 12 fl. oz.

Wyeth

WYETH Incorporated, Philadelphia 3, Pa.


Angiocardiography
Often indispensable, angiocardiography with Diodrast Concentrated Solution 70% has shown its greatest value in the diagnosis of
Coarctation of the aorta
Tetralogy of Fallot
Isolated pulmonic stenosis
Anomalous pulmonary veins
Aneurysms—congenital and acquired
Pericardial effusion
Syphilitic aortitis
Mediastinal tumors
Bronchogenic carcinoma
Used in thousands of cases, angiocardiography has become an established procedure. Write for booklet containing detailed information.
DIODRAST
CONCENTRATED SOLUTION 70%
AMPULS OF 50cc.
Winthrop Stearns INC
Diodrast, trademark reg. U. S. & Canada, brand of Iodopyracet



Depo-Heparin

price reduction of 26%

A price reduction of 26% makes it possible now for more patients to receive the therapeutic advantages of Depo*-Heparin.

Upjohn research and production workers have so improved methods of extraction, purification, and assay of this long-acting anticoagulant that it is now possible to meet increasing clinical needs and *to reduce its cost by 26%.*

Literature describing anticoagulant therapy in detail is available on request.

**Trademark, Reg. U. S. Pat. Off.*

Upjohn

Research ***in the service of the profession of medicine***

THE UPJOHN COMPANY, KALAMAZOO 99, MICHIGAN

℞ *Cabbages*

Once upon a time a blacksmith fell ill of a strange disorder. After eating a dish of cabbage, he fully recovered. Some weeks later his neighbor, the tailor, developed similar symptoms; cabbage was promptly administered but, alas, the tailor died. A would-be scientist in the village concluded that cabbage was a specific for the disorder, but *in blacksmiths only; for tailors* he pronounced it worthless and even dangerous.

The physician of today requires dependable evidence for the usefulness of his therapeutic agents. He also insists upon ***uniform, dependable purity*** for every drug that he uses.

For over 80 years physicians have relied on the ***uniform, dependable purity*** of **Mallinckrodt** products.

MALLINCKRODT PRESCRIPTION CHEMICALS

Iodides	Silver Salts
Bismuth Compounds	Mercurials
Iron Compounds	Salicylates
Diagnostic Aids	Mandelates
Sulfonamides	Vitamins

Anesthetic Agents

83 Years of Service to Chemical Users

MALLINCKRODT CHEMICAL WORKS

Mallinckrodt Street, St. Louis 7, Mo. • 72 Gold Street, New York 8, N. Y.
Chicago • Cincinnati • Cleveland • Los Angeles
Montreal • Philadelphia • San Francisco
Uniform, Dependable Purity

TERFONYL

Sulfadiazine
Sulfamerazine
Sulfamethazine

FOR SAFE SULFONAMIDE THERAPY

Low Renal Toxicity

With usual doses of Terfonyl the danger of kidney blockage is virtually eliminated. Each of the three components is dissolved in body fluids and excreted by the kidneys *as though it were present alone*. The solubility of Terfonyl is an important safety factor.

Terfonyl contains equal parts of sulfadiazine, sulfamerazine and sulfamethazine, chosen for their high effectiveness and low toxicity.

Terfonyl Tablets, 0.5 Gm. Bottles of 100 and 1000

Terfonyl Suspension, 0.5 Gm. per 5 cc.
Appetizing raspberry flavor · Pint bottles

SQUIBB PHARMACEUTICAL CONTRIBUTIONS TO THE MEDICAL PROFESSION SINCE 1858

TRADEMARK OF E. R. SQUIBB & SONS